In re GILEAD SCIENCES SECURITIES LITIGATION

This Document Relates To:

ALL ACTIONS.
SUMMARY AND OVERVIEW

1. Lead Plaintiffs Trent St. Clare and Terry Johnson ("Plaintiffs") bring this federal securities class action individually, and on behalf of a proposed class (the "Class") of all purchasers of the publicly traded securities of Gilead (NASDAQ: GILD) between July 14, 2003 and October 28, 2003, inclusive (the "Class Period"), against Gilead Sciences, Inc. ("Gilead" or the "Company") and certain of its top officers seeking remedies under the Securities Exchange Act of 1934 (the "Exchange Act").

2. Gilead, based in Foster City, California, is a biopharmaceutical company that discovers, develops, and commercializes pharmaceutical treatments for life-threatening diseases. According to Gilead's Forms 10-Q for the periods ending June 30, 2003 and September 30, 2003, the Company has six approved commercial products, including Viread, an antiretroviral agent used in combination with other drugs for the treatment of HIV infection. At all relevant times, Viread product sales are approximately 65% of Gilead's total revenues.

3. As stated in Gilead's Form 10-K for the period ending December 31, 2002 ("2002 10-K"), filed with the United States Securities and Exchange Commission ("SEC") on March 14, 2003, Gilead's commercial teams "promote Viread . . . through direct field contact with physicians, hospitals, clinics and other healthcare providers who are involved in the treatment of patients with HIV."

4. Throughout the Class Period, Defendants knowingly and affirmatively misrepresented the most important measurement of Gilead's performance and prospects to the investing public: the nature and cause of its increased sales of Viread. Wall Street analysts looked to sales of Viread, Gilead's most important and most promoted drug, to gauge whether the Company's business was on track and growing. If Gilead failed to publicly report healthy, growing Viread sales, its stock price would be greatly diminished.

5. Indeed, in an October 28, 2003 press release, Defendant and CEO John C. Martin ("Martin") addressed Gilead's need to obtain "higher prescription volumes" for Viread and identified the "important demand indicators" for Viread as being "new and total prescriptions." Thus, according to the 2002 10-K, Gilead had to "maintain and expand its position in the
“marketplace” (2002 10-K at 24) in the following areas: “efficacy; safety; tolerability; acceptance by
doctors; patient compliance; patent protection; ease of use; price; insurance and other reimbursement
coverage; distribution; marketing; and adaptability to various modes of dosing.” See 2002 10-K at
18.

6. In an October 27, 2003 Forbes article, Defendant Martin acknowledged that in order
for Gilead to reach its goal of increasing new and total prescriptions, it had to convince physicians to
switch patients from a competitor’s drugs to Gilead’s Viread drug regimen. According to the article,
Defendant Martin “concedes this is driven by marketing: ‘The AIDS market is driven by data.’”
Thus, according to the author, “Gilead, lacking a big ad budget, woos doctors by putting out a slew
of data showing Viread to be more effective than [competitor drugs], with fewer nasty side effects.”

7. In accordance with their business plan, Defendants made certain that Gilead reported
extremely impressive Viread sales results during the Class Period. Unfortunately for investors, these
results were attained through Defendants’ campaign of false and misleading promotional activities
for Viread found to be in violation of the Federal Food, Drug and Cosmetic Act and its
implementing regulations by the U.S. Food and Drug Administration (“FDA”). This off-label
marketing scheme materially (albeit artificially) increased Viread sales and created a false demand
for Viread. This skewed demand, in turn, motivated wholesalers to overstock massive amounts of
Viread in anticipation of an announced price increase.

8. To successfully implement their campaign of false and misleading promotional
activities, both prior to and during the Class Period, Defendants engaged in a systematic plan to
market Viread using clinical studies and other materials that had not received FDA approval and by
inducing Gilead sales and marketing representatives to make false and misleading statements
concerning Viread’s safety and efficacy to physicians, health care professionals and others. Such
tactics are generally referred to as “off-label marketing.” In doing so, Defendants minimized
important risk information regarding Viread, promoted Viread on the basis of unproven and untested
theories, and illegally “broadened the indication” for prescribing Viread to patients in violation of
FDA regulations by, among other things: (1) promoting it for use in patients with Hepatitis B co-
infection, despite the fact that it was not approved for such use; and (2) promoting Viread as an
“initial” or first-line treatment for HIV, even though, as discussed in more detail below, the FDA did not approve Viread for such treatment until late 2003. On two occasions, the FDA ordered Gilead to cease and desist this practice. Gilead blatantly ignored the FDA’s first warning (in a March 2002 FDA Untitled Letter) and thus received the second, more dire, warning from the FDA in July 2003 (during the Class Period). Defendants’ false, misleading, and illegal promotional practices resulted in materially increased sales of Viread during, at least, the Class Period.

9. Indeed, Gilead’s off-label and illegal promotional practices led to increased prescriptions which enabled Defendants to create the false and misleading impression that demand for Viread was much stronger than it actually was during the Class Period. As acknowledged by Defendants, increased Viread prescriptions were the primary indicator of strong Viread demand. Defendants, however, misled the market as to the true demand for Viread by failing to disclose that between 75% - 95% of all sales of Viread were caused by off-label marketing. Given Gilead’s domestic Viread sales of $115.6 million and $59.4 million during the second and third quarters of 2003, respectively, this means that between $86.7 million and $108.92 million (second quarter 2003) and between $44.5 million and $56.43 million (third quarter 2003) of domestic Viread sales reported during the Class Period were attributable to the off-label marketing scheme. In short, the market was not told that off-label marketing was the cornerstone of demand and defined the culture of the Company. This mistaken impression of demand led to, among other things, wholesaler overstocking in reaction to an anticipated price increase. When the truth about Defendants’ off-label marketing was disclosed, however, Defendants could no longer maintain the sales growth levels that investors had come to expect, and Gilead’s stock price dropped accordingly.

10. At the beginning of the Class Period, Gilead announced that overall sales doubled during Second Quarter of 2003, year-over-year, largely on the strength of Viread sales. The news caused Gilead’s stock price to rise $7.97 in one day, to a near-record high of $67.25.

11. However, securities analysts observed that the apparent strong demand for Viread resulted in part from wholesalers stocking up on the drug ahead of a price increase announced by Gilead in June 2003. The analysts were concerned that in future quarters demand for Viread would be met by inventory stocked by the wholesalers, rather than by new sales.
12. Indeed, in order to sell their stock at artificially inflated prices and to sustain the false and misleading impression that demand for Viread was strong, Defendants unequivocally rebutted the analysts' concerns. Defendants represented that the strong Second Quarter 2003 Viread sales were due to “an increase in prescriptions, not inventory stocking” and that “increased stocking by U.S. wholesalers accounted for $25-$30 million of Viread sales.” Because Defendants did not reveal that the “demand” for Viread was the result of off-label marketing, Defendants' rebuttal masked the fact that they would not be able to keep up sales growth at the same rate that investors had come to expect. Thus, as wholesalers drew down their overstocking in response to decreased demand, results would ultimately be worse than the market anticipated.

13. Defendants' inflated claims about Viread had their intended effect of maintaining Gilead's stock price long enough for Defendants to dump their Gilead shares on an unsuspecting market.

14. In just twenty-four days (between August 5, 2003 and August 29, 2003), Defendants sold in excess of 300,000 shares of Gilead stock at artificially inflated prices, reaping gross proceeds in excess of $20 million. This was the first and only time when all of the Defendants sold their stock during one coordinated time period. Notably, Defendants' selling spree took place just days after they had received FDA notification (sent to Gilead, care of Defendant Martin on July 29, 2003, but not made public until August 7, 2003) – for the second time since the launching of Viread – that their Viread promotional campaign and off-label marketing practices violated federal law. As set forth below, the disclosure of the existence of the FDA Warning Letter set in motion events that would impede Viread's sales growth and ultimately result in a sharp drop in Gilead's stock price.

15. At the end of the Class Period Defendants announced that sales of Viread in Third Quarter 2003 would be materially less than previously indicated. During the Third Quarter of 2003, wholesalers, responding to decreased demand for Viread after the disclosure of the FDA Warning Letter, drew down the entire amount of overstock and their existing supplies rather than purchase additional Viread. In short, demand for Viread was not nearly as strong as Defendants had led the market to believe.
16. In reaction to Gilead’s announcement of disappointing third quarter results, the price of Gilead stock plummeted, falling $7.46 in one day, from $59.46 per share on October 28, 2003, to $52 per share on October 29, 2003.

**JURISDICTION AND VENUE**

17. Plaintiffs bring this action pursuant to §§10(b) and 20(a) of the Securities Exchange Act of 1934 (the “Exchange Act”) (15 U.S.C. §§78j(b) and 78t(a)), and Rule 10b-5 promulgated thereunder (17 C.F.R. §240.10b-5).

18. This Court has jurisdiction over the subject matter of this action pursuant to §27 of the Exchange Act (15 U.S.C. §78aa) and 28 U.S.C. §1331.

19. Venue is proper in this District pursuant to §27 of the Exchange Act, 15 U.S.C. §78aa and 28 U.S.C. §1391(b). At all times relevant to this action, Gilead maintained its principal place of business in this District and many of the acts and transactions alleged herein, including the preparation and dissemination of materially false and misleading information, occurred in substantial part in this District.

20. In connection with the acts, conduct, and other wrongs alleged in this Complaint, Defendants, directly or indirectly, used the means and instrumentalities of interstate commerce, including but not limited to, the United States mails, interstate telephone communications, and the facilities of the national securities markets.

**THE PARTIES**

**Plaintiffs**

21. Plaintiffs Trent St. Clare and Terry Johnson purchased Gilead securities on the open market during the Class Period as set forth in their certifications previously filed with the Court. The Court’s January 30, 2004 Order appointed St. Clare and Johnson as Lead Plaintiffs in this consolidated action.

**Defendants**

22. Defendant Gilead, a Delaware corporation, maintains its principal place of business at 333 Lakeside Drive, Foster City, California 94404. Gilead is a biopharmaceutical company that discovers, develops, and commercializes therapeutics to advance the care of patients suffering from...
life-threatening diseases worldwide. The Company has six commercial products including Viread, an antiretroviral agent used in combination with other drugs for the treatment of HIV infection.

23. During the Class Period, Defendant Martin was the Company's President and Chief Executive Officer.

24. During the Class Period, Defendant John F. Milligan ("Milligan") was the Company's Chief Financial Officer and Senior Vice-President.

25. During the Class Period, Defendant Mark L. Perry ("Perry") was the Company's Executive Vice-President, Operations.

26. During the Class Period, Defendant Norbert W. Bischofberger ("Bischofberger") was the Company's Executive Vice-President, Research and Development.

27. During the Class Period, Defendant Anthony Carraciolo ("Carraciolo") was the Company's Vice-President.

28. During the Class Period, Defendant William A. Lee ("Lee") was the Company's Senior Vice-President, Research.

29. Martin, Milligan, Perry, Bischofberger, Carraciolo, and Lee (collectively the "Individual Defendants") were privy to non-public information concerning Gilead's business, finances, sales, products, product marketing and promotion, and present and future business prospects via access to internal corporate documents, conversations, and connections with other corporate officers and employees, attendance at sales management and Board of Directors meetings and committees thereof, and via reports and other information provided to them in connection therewith. Because of their possession of such information, the Individual Defendants knew or with deliberate recklessness disregarded the fact that adverse facts specified herein had not been disclosed to, and were being concealed from, the investing public. Except to the extent set forth in this Complaint as provided by confidential witnesses who are primarily former Gilead employees, Plaintiffs and other members of the Class had no access to such information, which was, and remains solely under the control of Defendants. The Individual Defendants were involved in drafting, producing, reviewing, and/or disseminating the materially false and misleading statements complained of herein. The Individual Defendants were aware (or disregarded with deliberate
recklessness) that materially false and misleading statements were being issued regarding the
Company and nevertheless approved, ratified, and/or failed to correct those statements, in violation
of the federal securities laws.

30. Throughout the Class Period, the Individual Defendants were able to, and did, control
the contents of the Company's SEC filings, reports, press releases, and other public statements. The
Individual Defendants were provided with copies of, reviewed and approved, and/or signed such
filings, reports, releases, and other statements prior to or shortly after their issuance and had the
ability and opportunity to prevent their issuance or to cause them to be corrected. The Individual
Defendants also were able to, and did, directly or indirectly, control the conduct of Gilead's
business, the information contained in its filings with the SEC, and its public statements. Moreover,
the Individual Defendants made or directed the making of affirmative statements to securities
analysts and the investing public at large, and participated in meetings and discussions concerning
such statements. Because of their positions and access to material non-public information available
to them but not the public, each of the Individual Defendants knew that the adverse facts specified
herein had not been disclosed to and were being concealed from the public and that the positive
representations that were being made were then false and misleading. As a result, each of the
Individual Defendants is responsible for the accuracy of Gilead's corporate releases detailed herein
as "group-published" information and is therefore responsible and liable for the representations
contained therein.

31. Each of the Defendants is liable as a primary violator in making false and misleading
statements, and for participating in a fraudulent scheme and course of business that operated as a
fraud or deceit on purchasers of Gilead securities during the Class Period. All of the Defendants had
motives to pursue a fraudulent scheme in furtherance of their common goal, i.e., inflating the trading
price of Gilead securities by making false and misleading statements and concealing material
adverse information. The fraudulent scheme and course of business was designed to and did: (i)
deceive the investing public, including Plaintiffs and other Class members; (ii) artificially inflate the
price of Gilead securities during the Class Period; (iii) cause Plaintiffs and other members of the
Class to purchase Gilead securities at inflated prices; and (iv) allow Gilead to conceal and cover up
the true financial condition of Gilead to the detriment of its investors, but to the financial benefit of
the Individual Defendants.

CLASS ACTION ALLEGATIONS

32. Plaintiffs bring this action as a class action pursuant to Federal Rules of Civil
Procedure 23(a) and (b)(3) on behalf of the Class, consisting of all those who purchased the
securities of Gilead during the Class Period. Excluded from the Class are Defendants, the officers
and directors of the Company, members of their immediate families and their legal representatives,
heirs, successors, or assigns and any entity in which Defendants have or had a controlling interest.

33. Because Gilead has millions of shares of stock outstanding, and because the
Company's shares were actively traded, members of the Class are so numerous that joinder of all
members is impracticable. As of February 27, 2004, Gilead had over 213 million shares outstanding.
While the exact number of Class members can only be determined by appropriate discovery,
Plaintiffs believe that Class members number at least in the thousands and that they are
geographically dispersed.

34. Plaintiffs' claims are typical of the claims of the members of the Class, because
Plaintiffs and all of the Class members sustained damages arising out of Defendants' wrongful
conduct complained of herein.

35. Plaintiffs will fairly and adequately protect the interests of the Class members and
have retained counsel experienced and competent in class actions and securities litigation. Plaintiffs
have no interests that are contrary to or in conflict with the members of the Class they seek to
represent.

36. A class action is superior to all other available methods for the fair and efficient
adjudication of this controversy, since joinder of all members is impracticable. Furthermore, as the
damages suffered by individual members of the Class may be relatively small, the expense and
burden of individual litigation make it impossible for the members of the Class to individually
redress the wrongs done to them. There will be no difficulty in the management of this action as a
class action.
37. Questions of law and fact common to the members of the Class predominate over any questions that may affect only individual members, in that Defendants have acted on grounds generally applicable to the entire Class. Among the questions of law and fact common to the Class are:

(a) whether Defendants violated the federal securities laws as alleged herein;

(b) whether Defendants’ publicly disseminated press releases and statements during the Class Period omitted and/or misrepresented material facts;

(c) whether Defendants breached any duty to convey material facts or to correct material acts previously disseminated;

(d) whether Defendants participated in and pursued the fraudulent scheme or course of business complained of;

(e) whether Defendants acted willfully, with knowledge or deliberate recklessness, in omitting and/or misrepresenting material facts;

(f) whether the market prices of Gilead securities during the Class Period were artificially inflated due to the material nondisclosures and/or misrepresentations complained of herein; and

(g) whether the members of the Class have sustained damages and, if so, what is the appropriate measure of damages.

CONFIDENTIAL WITNESSES

38. Plaintiffs’ allegations herein, concerning the falsity of Defendants’ statements and the scienter of the Individual Defendants, are based upon, in part, interviews with former Gilead employees, including former members of the Company’s sales and marketing staff. These witnesses, who spoke to Plaintiffs’ counsel on a confidential basis, are referred to herein as Confidential Witnesses (hereinafter, “CW”) numbers 1 through 8. The positions that the Confidential Witnesses held at Gilead permitted them to have direct access to the information provided by each, as described below.

39. CW1 worked as a Gilead Therapeutic Specialist from 2001 until approximately May 2003. As a Therapeutic Specialist, CW1 was responsible for promoting, marketing, and selling
Gilead products, namely Viread, and regularly had contact with and exposure to numerous Gilead executives and Regional Directors, including the Individual Defendants (with the exception of Carraciolo). CW1’s territory covered the Indiana, Illinois, and Michigan markets. In the course of his or her regular duties, CW1 worked with a variety of healthcare professionals, including physicians, nurses, social workers, and patients. In addition, over the course of CW1’s employment with Gilead, CW1 attended and participated in numerous national and regional Gilead meetings wherein Gilead executives specifically discussed the promotion of Viread. At these meetings, as well as at other times, Gilead provided CW1 with detailed information on Viread and told CW1 to use that information to aggressively promote and sell Viread. Among the information provided, however, was information not approved by the FDA for use in marketing and promoting Viread. Gilead executives provided this off-label information despite knowing that off-label marketing violated FDA rules and regulations. Further, at various times during CW1’s employment with Gilead, Gilead executives specifically instructed CW1 to teach and train other members of Gilead’s sales and marketing staff how to improperly and illegally use off-label information to market Viread.

40. Prior to the Class Period, CW1 was a member of Gilead’s Field Marketing Advisory Committee, a select committee of Gilead sales and marketing staff that periodically met to discuss theories and strategies for marketing and selling Viread. This elite group of Gilead employees was responsible for monitoring and shaping Gilead’s marketing efforts and advising Gilead’s management of the progress of those efforts. Members of Gilead’s sales and marketing staff from various regions of the country, as well as high-ranking Gilead officers and executives, including, but not limited to, Michael Inouye (“Inouye”), Gilead’s Senior Vice-President of Commercial Operations, James Meyers (“Meyers”), Gilead’s Vice-President of U.S. Sales, and various heads of marketing, such as Debbie Fletcher (“Fletcher”) and Sheryl Meredith (“Meredith”) attended the Field Marketing Advisory Committee meetings. As a result of CW1’s membership on the Field Marketing Advisory Committee, and CW1’s other contact and communications with numerous Gilead sales people, CW1 was very familiar with the sales tactics employed Company-wide and the impact of those tactics generally (and off-label marketing specifically) on Viread sales.
41. During the course of his or her employment, CW1 reported directly to Gary DelloStritto ("DelloStritto"), Gilead’s Regional Director for the Mid-West. In turn, DelloStritto reported to Meyers, Gilead’s Vice-President of U.S. Sales, who reported to Shay Weisbrich ("Weisbrich"), Gilead’s Vice-President of Sales and Marketing. Both Meyers and Weisbrich were members of Gilead’s Senior Management Team. Ultimately, Weisbrich was responsible to Inouye, Gilead’s Senior Vice-President of Commercial Operations and a member of the Executive Committee. Lastly, Inouye reported to the Individual Defendants, including Defendant Martin, and the Board of Directors.

42. CW2 worked as a Gilead Therapeutic Specialist from July 2000 until approximately February 2004. As a Therapeutic Specialist, CW2 was responsible for promoting, marketing, and selling Gilead products, namely Viread, and worked with a variety of healthcare professionals, including physicians, nurses, social workers, and patients in a manner similar to CW1. CW2 was, at various times throughout his or her tenure, responsible for covering the Georgia, South Carolina, and Alabama markets.

43. CW2 began his or her career at Gilead in the South sales region. During that time, CW2 reported to Bill Rich ("Rich"), Gilead’s Regional Director for the South. In turn, Rich reported to Meyers, who reported to Inouye. Lastly, Inouye reported to the Individual Defendants, including Defendant Martin, and the Board of Directors.

44. During CW2’s employment, CW2 also was a member of Gilead’s Dallas region and Southeast regions. While a member of Gilead’s Dallas and Southeast regions, CW2 reported to Kirk Kaiser ("Kaiser"), a Gilead Regional Director, and later to Charles Packard ("Packard"), another Gilead Regional Director. Kaiser and Packard reported to Rich. Rich, in turn, reported to Meyers. Finally, Meyers reported, at various times, to either Weisbrich or Fletcher (who replaced Weisbrich) and Inouye.

45. CW2 participated in pre-launch training for Viread, including, but not limited to, Gilead seminars and Gilead home-study materials. According to CW2, during the pre-launch period, Gilead was unsure whether the FDA would approve Viread and, if so, whether the approved indication(s) for Viread would be broad or limited. CW2 explained that if the FDA approved Viread
it could be for the use of Viread over a spectrum of indications from a “salvage” indication to an
“experienced” indication to a “naïve” indication. A “salvage” indication would limit Viread’s use to
patients with long-term HIV infection. An “experienced” indication would allow Viread’s use by
patients previously treated with other HIV drugs. Finally, a “naïve” indication would mean that
Viread could be used by patients recently infected with HIV but not yet exposed to a diverse
treatment regimen. The “naïve” indication is broader than the “experienced” indication and much
broader than the “salvage” indication. Gilead wanted a “naïve” indication which would allow for
much higher levels of Viread sales. CW2 estimates that seventy percent (70%) of AIDS drugs are
sold to “naïve” and “experienced” patients, while only thirty percent (30%) are sold to “salvage”
patients. CW2 also had a large amount of contact with CW2’s peers – other Viread sales people. In
fact, Gilead’s sales force, including CW1 and CW2, routinely shared information regarding their
sales tactics, the latest information being pushed by Gilead, and their sales. As a result, CW2 knows
that other sales people, at the insistence of Defendants, utilized off-label marketing and materially
increased Viread sales during the Class Period.

46. While awaiting FDA approval, and while not knowing what indication Viread might
receive, Gilead taught its sales staff to prepare to market Viread as though it had been approved with
the broadest possible indication. According to CW2, Gilead’s earliest plans included a scheme to
market Viread to “naïve” and “experienced” HIV patients regardless of the breadth of FDA
approval.

47. Over the course of his or her employment with Gilead, CW2, like CW1, attended and
participated in numerous national and regional Gilead meetings wherein Gilead executives
specifically discussed the promotion of Viread. At these meetings, as well as at other times, Gilead
executives provided CW2 with detailed off-label information for Viread and told CW2, both overtly
and covertly, to use that information to aggressively promote and sell Viread despite the fact that
those executives knew that such off-label marketing violated the FDA’s rules and regulations.

48. Nevertheless, despite his or her superiors’ pressure to market Viread utilizing off-
label materials, CW2 attempted to utilize off-label materials as little as possible. As sales people in
other areas of the country utilized off-label materials, however, the gap between sales in CW2’s
territory and other territories widened. Defendants then increased the already substantial pressure on CW2 to use off-label marketing. CW2 succumbed to this pressure, and did so in order to save his or her job and attempt to satisfy Defendants. Ultimately, CW2 terminated his or her employment with Gilead rather than follow these repeated directives to increase his or her use of off-label materials.\(^1\)

49. CW3 worked for Gilead from 2000 until January 2005. This former employee worked as a Gilead Therapeutic Specialist in the Washington state area, which included Seattle, Washington, from 2000 until late 2002. During this time, CW3 reported to Regional Director David McCullough (“McCullough”). As a Therapeutic Specialist, CW3 was responsible for selling Viread, Hepsera, and AmBisome.

50. In late 2002, CW3 was promoted to the role of Training Manager to replace Trainer Kristin Bennett (“Bennett”), who was promoted to the position of Senior Sales Director. Upon CW3’s promotion to Training Manager, CW3 began working at the Company’s Foster City, California headquarters. At the same time, another former Therapeutic Specialist was also assigned the role of Training Manager. Both CW3 and the other Training Manager reported to Meyers, the

\(^1\) In Plaintiffs’ Consolidated Amended Class Action Complaint for Violation of Federal Securities Laws filed April 30, 2004 [DE #50] (the “CAC”), it was alleged that CW2 refused her/his “superiors’ ever-increasing pressure to market Viread utilizing off-label materials” and “terminated his or her employment rather than follow these questionable directives to use off-label materials.” CAC at ¶50. This allegation incorrectly implied CW2 never promoted or sold Viread with off-label information. Subsequent to the Court’s January 26, 2005 Order [DE #98] dismissing without prejudice the CAC, as part of Plaintiffs’ ongoing investigation, CW2 continued to describe her/his experiences at Gilead. During this time, CW2 clarified what she/he meant by CW2’s “refusal” to bow to her/his superiors’ ever-increasing pressure to market Viread with off-label information, and provided further explanation and factual detail concerning her/his resignation from Gilead. CW2 stated that she/he had no choice but to engage in off-label marketing while at Gilead. CW2, however, was never comfortable doing so because CW2 knew off-label marketing was illegal. Gilead management and CW2’s superiors, however, pressured CW2 to utilize more and additional off-label materials. Put simply, CW2 was told she/he was not being aggressive enough with her/his use of off-label information to sell Viread and had to do more. Rather than kowtow to this additional pressure, CW2 left the Company. Thus, when CW2 stated that she/he refused to bow to “ever-increasing pressure” to market Viread using off-label information, CW2 did not mean she/he never used off-label information, but that she/he refused to increase her/his use of off-label information to sell Viread. Viewed in this light, allegations attributed to CW2 in the CAC and the Fourth Amended Consolidated Complaint (“FAC”) are not contradictory. If anything, the original allegations in the CAC were inartfully drafted. To the extent the Court concludes they are conflicting, however, CW2’s last word to Plaintiffs’ counsel regarding sales of Viread and the reason why she/he left Gilead is reflected in the allegations of the FAC.
Company’s Vice President of U.S. Sales. Around the time CW3 was promoted to the role of Training Manager in late 2002, the Company’s sales force was divided up so that there were dedicated Therapeutic Specialists selling Viread and different Therapeutic Specialists selling Hepsera and AmBisome. From the time CW3 was promoted to Training Manager until she/he left the Company in 2005, CW3 was tasked with developing training materials for HIV Therapeutic Specialists – both incumbent and incoming Gilead sales representatives.

51. CW3 emphasized there was a pervasive, covert strategy throughout her/his tenure with Gilead to market Viread off-label and that this strategy was executed from the top-down. While working as a Therapeutic Specialist, CW3 promoted Viread for off-label indications using materials provided by CW3’s superiors, which CW3 understood had been distributed to all of the HIV Therapeutic Specialists at Gilead for sales purposes. She/he stated that during the Class Period, Viread was promoted off-label for a treatment naïve indication, as well as for a Hepatitis B indication, and as having a better safety profile than was actually the case. CW3 stated the FDA, at the time, did not approve or allow any of this information to be used to sell Viread.

52. CW3 recalled there was widespread, covert encouragement by senior Company management to promote Viread off-label, and that off-label information and data was used by Therapeutic Specialists in sales calls throughout CW3’s tenure. Among many other things, CW3 recalled that materials were presented and distributed to the Company’s sales force at Gilead’s national and regional sales meetings, and that these materials contained facts about the efficacy of Viread for treatment naïve patients and for the treatment of Hepatitis B – namely for co-infected patients. For example, CW3 stated that sales of Viread for use by treatment naïve patients represented a “large portion” of Viread sales before and during the Class Period, which resulted from Gilead’s off-label promotion of Viread for such purposes. As a Therapeutic Specialist, CW3 experienced first-hand Defendants’ off-label marketing scheme, and stated the strategy to promote Viread off-label was definitely covert, but also definitely one that spanned the ranks of the Company’s sales and marketing departments, and defined the culture of the Company.

53. In her/his role as a Training Manager, CW3 was tasked with, among other things, writing-up materials for use by the Company’s Therapeutic Specialists in their presentations to
doctors that contained both information approved by the FDA and unapproved off-label information from recent conferences and studies. CW3 stated that because Gilead’s marketing department could not directly tell the sales force to market off-label, Gilead used the training department to deliver marketing’s message. The result was that Gilead HIV Therapeutic Specialist training materials, including throughout the Class Period, contained a great deal of off-label information, and these training materials were provided to the Company’s sales force specifically for use as talking points with the doctors on which they called. In addition, Meyers directed CW3 to write training materials for the Therapeutic Specialists that contained bullet points layered not only with FDA-approved data, but also with unapproved, off-label data and information. As a result, the Company’s sales force was deliberately being trained and encouraged – from the highest levels – to engage their existing and potential clients in off-label discussion regarding Viread using information in the documents they received from the Company. Put simply, the internal Company strategy to sell Viread relied extensively on off-label information and data.

54. CW3 also stated that from at least the time CW3 was promoted in late 2002 through at least January 2005, there were weekly internal Gilead meetings to discuss the provision of off-label material to the Company’s HIV sales force. These meetings were held in a conference room at the Company’s home office in Foster City, California, and attendees at the meetings included the marketing and training department heads, the sales directors, and Meyers was typically brought in at the end of each meeting. The result of the meetings was that Meyers supported the notion that Therapeutic Specialists should receive off-label marketing materials, and directed the provision of such materials to be accomplished through the Company’s training department. In other words, the training department’s role in the Company’s off-label marketing strategy would be to deliver marketing’s off-label message. CW3 described her/his own specific role in the provision of off-label materials as part of the “whole wink and nod” process to give Gilead’s sales team information they needed to market and sell Viread off-label.

55. By 2005, CW3 could no longer tolerate the ongoing unethical sales practices and consistent pressure to engage in the Company’s illegal, off-label strategy to sell Viread. Put simply, the regular and constant internal pressure for CW3 to be the messenger of the Company’s illegal off-
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label marketing strategy became too much to bear. Rather than continue on the path cut by
Defendants, CW3 left the Company.

56. CW4 was one of the members of the first group of Medical Science Liaisons to work
for Gilead. CW4, a Ph.D., began her/his employment with the Company in approximately 1999 and
was asked to leave the Company in approximately January 2003, when it was apparent CW4 was not
willing to comply with some of the requests of the Company’s senior management and sales
organization to promote Viread in a biased, off-label manner. CW4 was hired by and initially
reported to Vice President of Marketing Bruno Delagneau (“Delagneau”), who oversaw Gilead’s
Medical Science Liaisons until he was reassigned within Gilead. Steve Barriere (“Barriere”)
replaced Delagneau for approximately six months, at which time Barriere was removed and replaced
by Chris Garabedian (“Garabedian”).

57. CW4 stated Gilead promoted Viread off-label via presentations the Therapeutic
Specialists made to medical practitioners, as well as through encouraging the Medical Science
Liaison staff to act in a sales capacity, including presenting biased and unbalanced information about
Viread. CW4 stated Viread was promoted off-label for a treatment naïve indication, a Hepatitis B
indication, and as having a better safety profile than data suggested was actually the case. CW4 was
aware that Therapeutic Specialists promoted Viread off-label based on her/his participation in
meetings the Therapeutic Specialists had with HIV treating physicians. She/he stated that most of
the Therapeutic Specialists who marketed Viread utilized off-label information, including through
the use of documents provided to them by higher-level Gilead employees in briefing binders the
sales force received at national Company meetings. CW4 emphasized that during the Class Period,
government rules dictated the Therapeutic Specialists were not supposed to ask leading questions
that could potentially result in an off-label discussion and were not legally allowed to talk about
published data that had not been approved by the FDA. In other words, the rules were that Gilead’s
sales force was supposed to stay on-label. For example, if a practitioner had an off-label question,
the Medical Science Liaisons were supposed to answer such questions in lieu of the Therapeutic
Specialists, and were supposed to provide unbiased information about Viread. But, CW4 stated that
“all of the [sales] reps” engaged in off-label detailing of Viread, and answered off-label questions on
their own without involving the Medical Science Liaison staff. Towards the end of her/his tenure with Gilead, CW4 recalled there were only approximately two Therapeutic Specialists who would excuse themselves from the discussion between their customers and CW4 when the subject turned to off-label areas — even though this should have been standard protocol so that the sales staff was not trying to close a sale with the help of the Medical Science Liaison staff.

58. On top of the foregoing, CW4, even though she/he was a Medical Science Liaison, was tasked with selling Viread at least 75% of the time, which was not consistent with what CW4’s role should have been as a member of the medical affairs organization at Gilead. Instead of only presenting data at dinner meetings and Company meetings, and being available to address questions posed by investigators working on trials related to Viread or who were potentially interested in doing so, CW4 worked in a sales capacity. In this role as a Viread salesperson, CW4 was asked to promote Viread off-label. For example, the Medical Sciences Liaisons were encouraged to present data in a biased manner — namely in a manner that was not only off-label, but also made Viread appear to have a wider indication and a better safety profile than was actually the case. The pressure for the Medical Science Liaisons to act in a sales role and to present biased and off-label data for Viread while acting in a sales role came from the highest levels of senior management at Gilead. CW4 stated that Martin, the Company’s CEO, led the off-label detailing strategy regarding Viread. CW4 also stated the Company’s strategy to market Viread off-label was very covertly executed. She/he stated there was an “obvious push by top management,” including Martin, to involve the Medical Science Liaisons in marketing and sales, including off-label sales of Viread. She/he stated that most of the Therapeutic Specialists complied with the Company’s off-label marketing strategy — i.e., they promoted and sold Viread with off-label information. CW4 stated those Therapeutic Specialists and, especially, the Medical Science Liaisons who were not willing to toe the Company line and follow Defendants’ off-label selling strategy were ousted from the Company. These employees were shown the door and told they did not meet the Company’s requirements.

59. CW4 was presented with an offer to leave Gilead in approximately 2003 because CW4 was not willing to promote biased “investigator initiated trials” for Viread led by Sales Director Helen Harris’ staff. CW4 and her/his colleagues were replaced by medical doctors who
CW4 and her/his colleagues had formerly been calling on in their Medical Science Liaison roles to promote Viread. The Medical Science Liaisons that replaced CW4, Sass, and Childs included Bruch Olmscheid ("Olmscheid"), Al Fisher ("Fisher"), and Stuart Burstin ("Burstin").

60. CW5 worked for Gilead from 2001 through 2005, and is a former Therapeutic Specialist and Training Manager. CW5 was promoted to the role of Training Manager in late 2002. This former employee experienced the Company's off-label marketing scheme for Viread, and has knowledge concerning how it was implemented. CW5 stated there was a culture at Gilead that promoted and condoned off-label marketing of Viread throughout the Class Period. She/he based this statement on the fact that she/he had a lot of experience with the Company, first "in the field" and later in the corporate training role where she/he worked on the development and distribution of training materials for the sale of Gilead pharmaceuticals, including Viread. Based on her/his experiences with Gilead, CW5 stated the Company's strategy to market Viread off-label was developed and driven from the top executives, including the Vice President of U.S. Sales, Meyers.

61. For example, CW5 stated the Gilead HIV Therapeutic Specialists were provided with off-label marketing materials for use in promoting Viread, as well as being trained to be very aggressive in their sales pitches. CW5 recalled receiving off-label promotional materials that were not marked as being confidential or not for promotional use. When promoting Viread, the Company's Therapeutic Specialists were allowed and encouraged to use these materials in discussions with doctors.

62. Through discussions with the Company's Vice President of U.S. Sales, Meyers, CW5 learned that one way Gilead executed its off-label promotion strategy was through instilling the notion that the sales team members were "specialty care representatives" and that they were thus not limited to talking about just what was in the package insert for Viread. Meyers informed CW5 in discussions that as "specialty care reps," the Gilead Therapeutic Specialists were expected to be equipped and willing to engage in off-label discussion about Viread.

63. CW5 recalled there was a slide presentation developed by Meyers and presented by Rich, the Regional Director for Gilead's South Region, in April 2003. One particular slide in the presentation centered on the strategy to promote Viread off-label, and included details about
Gilead’s efforts to use Medical Science Liaisons in a sales capacity to promote Viread off-label.

This slide was shown at a sales meeting attended by the Southwest and Northeast Region sales team members and was part of a presentation detailing Gilead’s strategy for “re-launching” Viread and bridging the gap between a slowdown in sales of Viread that had occurred prior to April 2003 and when Gilead anticipated receiving approval for the treatment naïve patient indication. CW5 stated the presentation may have also been made to new hires at the Company who were tasked with selling Viread and who were hired by Gilead during the first half of 2003.

64. CW5 stated the slide in question indicated that the Company needed to promote Viread to HIV doctors who were using it to treat Hepatitis-B – even though such promotional practices and concomitant sales were 100% off-label and illegal. CW5 stated the slide concerned the threat to Viread sales, meaning that the reason for the presentation in April 2003 was to deliver the message that sales of Viread were being threatened by HIV drugs developed and marketed by Gilead’s competitors and that Gilead needed to market Viread for off-label indications as a means to overcome that threat. CW5 stated the Company’s sales force was anxious to make sales and goose up Gilead’s stock price, and thus were amenable to management’s demand to sell off-label. Now that CW5 has left Gilead, however, she/he sees how egregious behavior was the norm at Gilead.

65. CW5 stated another example of the emphasis on off-label marketing at Gilead was the briefing binders or “poster books” put together for the sales force by the Company’s trainers and sales managers. The briefing binders were comprised of abstracts collected from recent (at the time) medical conferences and other literature supporting and promoting Viread for various off-label indications. Trainers used these briefing binders, which doubled as visual aids, to teach sales representatives how to sell Viread for off-label uses. These “poster books” were provided to the Viread Therapeutic Specialists for use in the field, and the documents in them did not bear markings rendering them confidential or not for promotional purposes. CW5 stated the documents went beyond information approved by the FDA and the use of the “poster books” in field visits with practitioners constituted off-label marketing. She/he stated this off-label strategy was executed in such a manner that the Therapeutic Specialists would not only be equipped with materials to promote
Viread off-label, but also with the understanding that they were expected to promote the drug for off-label indications.

66. CW5 recalled that some sales representatives balked at the Company's off-label strategy for sales, but Meyers told CW5 directly that Defendant "John [Martin] would have people's heads on a platter if they didn't sell this way." Meyers was always telling CW5 to promote off of the data that was coming out of the conferences – i.e., the off-label, non-FDA approved data. CW5 stated Gilead was a data-driven company, and the sales force was taught to sell from the off-label data. CW5 recalled that Meyers was duplicitous and would not say anything about off-label marketing at the Company's conferences, but was a very different person behind closed doors.

67. CW6 worked as a Therapeutic Specialist at Gilead from March 2003 until January 2006. CW6 marketed HIV pharmaceuticals to hospitals, clinics, and physicians in the Brooklyn and Queens, New York area. She/he recalled that the Company's VP of Sales, Meyers, was engaged in highly unethical behavior and served as a conduit for directives from the highest levels of the Company.

68. With regard to off-label uses, CW6 recalled receiving and using off-label materials "all the time" in sales presentations, and stated the Company's sales representatives were routinely provided with papers or studies supporting one or another off-label use. She/he stated off-label marketing was known by everyone to comprise a core component of the Company's marketing and sales for Viread. For example, CW6 stated that in 2003 and 2004, it was well-known through the Company's sales representatives that marketing to Hepatitis B patients was an alternative means of marketing and selling Viread.

69. CW6 stated the use of off-label materials in sales presentations was prevalent for Viread, and confirmed that off-label materials were included in a binder distributed within the Company to sales representatives. To ignore those off-label materials would be to consign yourself to a far more limited (albeit legal) market. She/he stated many conferences held around the world generated abstracts and other materials describing small or informal studies and other information relating to the use of Viread for Hepatitis or treatment naïve patients. These studies were often made
up of only 30 to 40 patients, or were Phase II studies. CW6 stated Company sales people would "use those studies to suggest whatever we were trying to convey at the moment."

70. CW6 recalled that although many off-label materials had "For Educational Purposes" stamped on the bottom, it could be easily covered up when reproducing the document. In fact, she/he said that such a designation was a "joke" and that her/his boss was well aware how such materials were used and why. One reason was enormous pressure to make sales. CW6 stated that the Viread sales staff was driven by Company management to improve sales numbers for publication to a national marketplace.

71. Among other things, CW6 has knowledge of how off-label materials were presented to doctors during sales calls, and how the Company sought to take advantage of treatment naïve patients before receiving FDA approval for that indication because treatment naïve patients offered the longest potential users of Viread. For example, she/he recalled the Company’s sales force sold Viread first line (i.e., to treatment naïve patients) all the time and that if they did not do so, they would have been fired from Gilead. CW6 recalled using non-FDA approved study data to promote Viread as a first-line therapy to treatment naïve patients, and stated that easily 70% of her/his Viread sales were attributable to off-label treatment naïve patients.

72. CW7 was a former Therapeutic Specialist and Trainer for Gilead in Dallas, Texas who was with the Company from prior to 2002 until approximately 2006. CW7 estimated that, with regard to Hepatitis-B infected patients, 10% of her/his total Viread sales were off-label to treating physicians. CW7 believes the Company also was promoting Viread off-label in the pediatric population. CW7 estimates that her/his sales to a pediatric population were about 10% of her/his total sales. Thus, in these two patient segments alone, 20% of CW7’s total Viread sales were completely off-label. While CW7 did not actively pursue off-label sales in other areas, she/he stated that other sales representatives were feeling pressure to engage in off-label marketing to boost their sales. CW7 stated that a key culprit in getting the off-label message out was Rich, Gilead’s Regional Director of Sales for the South.

73. CW8 was a former Gilead Therapeutic Specialist from April 2003 until mid-2008. CW8 recalls that early in the launch of Viread, sales representatives were instructed to promote
Viread to Hepatitis B doctors because it was active. She/he explained that “active” in a pharmacologic context means that a chemical agent has activity against a certain infective agent, and Hepatitis B was an infective agent. CW8 recalled that because there was data showing Viread was active against Hepatitis B, Gilead’s training materials supported that it was active and managers informed the sales force that it was part of management’s expectation that this information would be communicated on sales calls. The indisputable fact that Viread had not been cleared by the FDA for this use was not part of the discussion; the discussion was that the product was “active.” CW8 also stated that co-infected patients with Hepatitis-B and HIV were considered to be easy sells at Gilead. She/he recalled that Martin would refer to Viread as a miracle product all the time at meetings, which suggested to those listening that they could use that language out in the field when selling Viread to doctors. CW8 recalled that Gilead’s sales force had “little if any regulatory training” and was not discouraged from repeating off-label medical claims espoused by Martin at sales meetings.

FACTUAL DETAIL UNDERMINING THE TRUTH OF DEFENDANTS’ CLASS PERIOD REPRESENTATIONS

A. Gilead’s Fraudulent Off-Label Marketing Campaign

FDA Prohibitions

74. The Federal Food, Drug, and Cosmetic Act, and its implementing regulations, 21 U.S.C. §301, et seq., set forth the manner in which a pharmaceutical manufacturer is permitted to market and promote its products. According to these guidelines, a pharmaceutical manufacturer may only promote an FDA approved drug consistent with the contents of the drug’s official package labeling (the “Package Labeling”). See 21 C.F.R. §202.1. To ensure that pharmaceutical companies comply with these rules, the FDA monitors and enforces the Federal Food, Drug, and Cosmetic Act through its Division of Drug Marketing, Advertising, and Communications (the “DDMAC”).

75. In their public statements, Defendants emphasized that their business plan placed great importance on their careful compliance with these federal and state regulations. For example, in Gilead’s 2002 10-K, Defendants stated:

In the U.S., drugs are subject to rigorous FDA regulation. The Federal Food, Drug and Cosmetic Act and other federal and state statutes and regulations govern the
testing, manufacture, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion of our products. ... We are required to demonstrate the safety and effectiveness of products we develop in each intended use through extensive preclinical studies and clinical trials in order to obtain regulatory approval of these products.

76. Based upon FDA rules and regulations, each of Gilead’s FDA-approved drugs is accompanied by prescribing information provided to doctors prescribing and patients using the drug (the “Prescribing Information”). The FDA approves every word of the Prescribing Information, which is part of the Package Labeling. The Package Labeling thus provides information about the drug, its approved and intended uses, and a description of its side effects. The Package Labeling is vital to a physician’s determination of whether to prescribe the drug. Indeed, the Physician’s Desk Reference (“PDR”), the standard guide to prescription drugs for physicians and other healthcare professionals, reproduces the FDA approved prescribing information and labeling to allow physicians, pharmacists, and other medical professionals to correctly use prescription drugs to treat their patients.

77. Because the information contained in the Package Labeling is based upon medical studies and scientific data submitted to and approved by the FDA, it is used by physicians to determine whether a drug can be effectively used and safely tolerated by their patients. The FDA prohibits pharmaceutical manufacturers’ sales and marketing representatives from promoting prescription drugs with information not found in the Package Labeling. As such, use of non-FDA approved materials is referred to as “off-label” marketing.

78. For example, it would be considered off-label for a company to market a FDA-approved HIV/AIDS drug as also being effective for fighting Hepatitis B infection (which, as discussed in more detail below, Gilead illegally did with Viread) if such use of the drug had not been reviewed and approved by the FDA and included in the Package Labeling. So long as the Package

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2 Hepatitis B is a serious disease caused by a virus that attacks the liver. The virus, which is called hepatitis B virus or HBV, can cause lifelong infection, cirrhosis (scarring) of the liver, liver cancer, liver failure, and death.
Labeling lacks information regarding the HIV drug’s ability to fight Hepatitis B infection, the company’s sales representatives are not permitted to speak about this to their customers.

79. The only exception to this rule is if a physician or other medical professional specifically requests such information first, via a signed written form. For example, a physician may be treating a patient who has both HIV and Hepatitis B co-infection. While treating the patient, the physician may notice that the patient’s HIV medication appears to positively impact the patient’s Hepatitis B infection symptoms. In such a situation, if the doctor submits a written request to the drug manufacturer, typically by utilizing a Gilead inquiry form (the “Inquiry Form”), the drug manufacturer may provide the doctor with results of studies which detail the drug’s interaction with Hepatitis B infection, even if those results are not FDA approved or found in the Package Labeling. See Exhibit A attached hereto (a true and correct copy of a Gilead Inquiry Form). The company sales representatives are not permitted to initiate conversation or promote this to their customers.

80. Without such a request it is a direct violation of FDA rules and regulations for a drug company to provide its customers with off-label information. And yet, according to the Confidential Witnesses, Defendants encouraged and expected Gilead’s sales and marketing staff to do exactly that, and then – after the fact – obtain an Inquiry Form to create the appearance of propriety.

81. Moreover, Defendants trained Gilead’s sales force to purposely misuse off-label information in order to boost sales and gain an advantage over competitors. Indeed, as set forth below, the Company specifically used its training department to deliver the Company’s off-label message for Viread to Gilead’s sales force.

82. While companies are permitted to promote their products with information found in the Package Labeling, Gilead, as part of its scheme to artificially boost Viread sales, repeatedly exceeded this recognized limitation set by the FDA to promote Viread. Specifically, since prior to the launch of Viread, Gilead implemented a scheme to promote and market Viread with off-label, false, and misleading statements in violation of the Federal Food, Drug, and Cosmetic Act. In order to gain market share, artificially increase perceived demand, and increase sales, Gilead officers, executives and clinical personnel, with the express knowledge and approval of the Individual Defendants, routinely and consistently provided Gilead’s sales and marketing team with off-label
information and encouraged, expected, and directed them to use it to sell Viread even without the
written request of a medical professional. Gilead’s sales and marketing strategies, as well as its
entire corporate culture, rested heavily on selling Viread by way of off-label, unapproved
information.

83. According to CW1, in an effort to win FDA approval for Viread, Gilead submitted to
the FDA a book of Viread clinical data and information, entitled the FDA Advisory Committee
Briefing Document (the “FDA Briefing Document”). See Exhibit B attached hereto (a true and
correct copy of the FDA Briefing Document). The FDA did not include all of the information found
in the FDA Briefing Document in Viread’s Package Labeling. For example, the FDA Briefing
Document contained information regarding Viread’s impact on bone density and the incidence of
bone fracture resulting from Viread use. Because the FDA withheld such information from the
Package Labeling, Gilead’s sales team was prohibited from marketing Viread as being superior to
other HIV drugs with regard to bone density issues.

84. CW1 confirmed that Gilead submitted the FDA Briefing Document to the FDA
because, in September 2001, while attending a company-wide national meeting in Miami, Florida
(the “Miami National Meeting”) CW1 and other members of Gilead’s sales and marketing team
viewed, via teleconference, Gilead’s executives and clinical researchers presentation to the FDA
Advisory Committee in Washington, D.C. In addition, while at the Miami National Meeting, CW2
confirmed the substance of the materials Gilead’s executives covered during the teleconference.

85. According to both CW1 and CW2, among those present at the Washington, D.C.
FDA presentation were Defendants Martin, Perry, Lee, and Milligan. All in attendance at the FDA
briefing were aware that Gilead’s sales and marketing staff was watching the presentation via
teleconference at the Miami National Meeting. CW4 also attended the meeting with FDA
representatives in Washington, D.C., and recalls Defendants Martin and Bischofberger being in
attendance. CW4 stated Gilead had extensive data to support an “experienced” indication for
Viread, but expected to receive naïve indication approval at the FDA meeting. Viread, however, was
only initially approved as an “experienced” treatment option.
86. The Miami National Meeting teleconference was attended by, among others, Meyers, Weisbrich, and Fletcher. According to CW1 and CW2, the purpose of the teleconference was to allow Gilead's salespeople and marketing department to become familiar with the FDA Briefing Document and related materials in order to market Viread, regardless of the FDA's approval and indication assigned to Viread.

87. After making their presentation to the FDA, Gilead's officers, executives, and clinical personnel, including Inouye and Defendants Martin, Milligan, Perry, and Bischofberger traveled to the Miami National Meeting already in progress. CW1 and CW2 specifically recall that, while at the Miami National Meeting, Gilead representatives provided them and other Gilead sales and marketing staff with off-label marketing information and, with a "wink and a nod," instructed them to use it to sell Viread. CW1 and CW2 specifically recall Defendant Martin attending those same meetings in Miami and physically being at meetings during which Gilead's sales and marketing team members were given their marching orders.

88. Importantly, at the time of the FDA presentation, according to CW1, the FDA had not approved any of Gilead's clinical studies or theories for Viread. Thus, everything discussed at the Miami National Meeting, and not later included in the Package Labeling, was off-label.

89. Although Gilead's clinical researchers created the FDA Briefing Document for the FDA, the entire book was intentionally provided to at least some of Gilead's sales and marketing team at the Miami National Meeting in September 2001. DelloStritto, CW1's supervisor and Gilead's Regional Director for the Mid-West, instructed CW1 to make numerous copies of the FDA Briefing Document and distribute it to various members of Gilead's Viread sales and marketing team. According to CW1, the sole purpose of Gilead instructing him or her to do so was to provide it to Gilead's sales force so that they could market Viread with off-label information in order to increase sales.

90. Thus, even before the FDA approved Viread one month later (October 2001), Gilead representatives and employees planted the seeds of fraud by circulating off-label information to artificially boost sales of Viread.
91. In that regard, CW4 stated that despite the lack of approval for Viread for treatment naïve HIV patients, marketing Viread as a treatment option for treatment naïve patients was very much a part of the Company’s strategy. For example, CW4 recalls that during the role play sales training sessions that she/he attended, including at the Company’s national sales meetings, one question that was posed to Therapeutic Specialists as part of their training and preparation (as if the question was coming from a customer or infectious disease practitioner) was “why should I not use it [Viread] for naïve patients?” The Therapeutic Specialists were trained to answer the question in a manner that effectively informed the HIV doctor that he or she should use Viread for a naïve indication and that there was no reason to not use Viread for a naïve indication. CW4 stated this strategy to market Viread for a naïve indication, despite the lack of FDA approval for such during the Class Period, came down from the highest levels of Company management, including from Defendant Martin.

92. Similarly, CW6 stated the Company sought to take advantage of the treatment naïve patient group because it offered the patients who would take Viread for the longest period of time (and thus sustain Viread sales). She/he stated the Company and its sales staff always pushed for treatment naïve patients because they would remain on their first regimen of HIV drugs for a long period of time. Gilead did this despite the fact that, at the time, there was no indication for use of Viread as a first-line HIV therapy. CW6 stated the Company sold Viread as an initial therapy all the time, and that if members of the sales staff did not do so, they would be fired. CW6 recalled, among other things, using various non-FDA approved study data to support Viread’s use in treatment naïve patients and that the sales staff had visuals, marketing pieces, and visual aids of off-label information from the ongoing studies.

93. Gilead and the Individual Defendants, at all relevant times (including prior and subsequent to the Class Period), knew that off-label marketing of Viread was improper. Hence, to cover its tracks, Gilead often combined its “wink and a nod” directives to its sales force (including providing off-label materials for use by its sales force) with meaningless, perfunctory reminders that such off-label materials should not be provided to Gilead’s customers. CW4 confirmed that Defendants tried to cover their tracks, knowing that outward directives to promote Viread for off-
label use would get them in trouble. Instead, CW4 said there was a more discreet effort to implement the strategy to promote Viread for off-label use.

94. Gilead, in effect, tried to cover its tracks by directing, expecting, and encouraging off-label marketing but combining those directives with a paper trail that could be used in the event they were ever caught. Since Gilead’s scheme of illegal marketing has now been exposed, and Gilead has been caught, it will no doubt turn to its paper trail in order to attempt to avoid liability. This Court should anticipate this and not be fooled.

95. One example is that one of Gilead’s common tactics was to circulate to its sales staff a cover memorandum with off-label materials attached. The body of the cover memorandum would say that the materials were for “internal use only,” but the actual off-label materials would conspicuously not contain any such limiting language. See Composite Exhibit C attached hereto (true and correct copies of internal Gilead documents demonstrating this practice). The sales and marketing staff was then directed, expected, and encouraged to remove the cover memorandum and use off-label materials to promote Viread. Indeed, CW1 recalls being told by DelloStritto not to let such off-label materials get into the hands of unintended recipients because it was illegal for CW1 and other Therapeutic Specialists to use that information.

96. CW3 stated that while she/he worked as a Therapeutic Specialist, materials were presented and distributed to the Gilead sales force at national and regional sales meetings, and the materials contained facts about the efficacy of Viread as a drug for treatment naïve patients, and for treatment of Hepatitis B (namely co-infected patients). CW3 also stated the sales force received updates on studies that supposedly validated the use of Viread for off-label indications. This experience was echoed by CW1, CW2, CW4, CW5, and CW6. Similarly, CW8 recalled receiving training materials that included off-label uses. While CW3 was not directly told to use the marketing materials she/he received, she/he emphasized that “everything was provided to the reps that they needed” to promote Viread off-label and there was widespread, covert encouragement by senior management for Therapeutic Specialists to use such data in sales calls – which they did throughout CW3’s tenure. For example, CW3 stated sales of Viread for use by treatment naïve patients represented a “large portion” of the sales of Viread before and during the Class Period, which
resulted from Defendants’ off-label marketing scheme. While CW3 stated Defendants’ off-label sales strategy was definitely covert, it also definitely spanned the ranks of the sales and marketing organization and defined the culture of the Company.

97. CW3 recalled Defendant Martin routinely speaking off-label about Viread at internal and external meetings. CW3 attended meetings with the key opinion leaders in her/his territory, along with Martin. She/he believed there were at least 3 meetings in the Seattle, Washington area while CW3 worked as a Therapeutic Specialist during which Martin spoke off-label about Viread to key opinion leaders. In particular, Martin recounted results of a Viread study in which a certain type of monkey had been injected with SIV or HIV, and that approximately 48 hours after being injected with the virus, the monkeys were given a high dosage of Viread and subsequent tests showed they did not contract the virus with which they were injected. Martin used these study results to promote Viread off-label and to effectively suggest Viread had increased potency beyond what was indicated in its Package Labeling.

98. In December 2001, Gilead hosted a weeklong national meeting for its employees at the Phoenician Hotel in Scottsdale, Arizona (the “Arizona National Meeting”). CW1 and CW2 attended this meeting, the purpose of which was to celebrate the FDA’s approval of Viread and ready the Company for an aggressive and illegal marketing campaign using off-label materials.

99. During the Arizona National Meeting, CW1 and CW2, along with numerous other members of Gilead’s sales and marketing staff, attended several Viread marketing presentations. CW1 and CW2 specifically recall Defendants Martin, Milligan, and Perry attending these meetings. During these marketing presentations, Gilead provided the sales staff with updates regarding ongoing Viread clinical trials, the results of which, until approved by the FDA, were off-label.

100. In addition, CW1 and CW2 recall attending Arizona National Meeting presentations during which they, and numerous other Gilead sales and marketing staff, received updates concerning various clinical trials, including Study 903 and Study 907. They also participated in discussions regarding Viread’s resistance profile and potential use to combat Hepatitis B infection, even though Viread had (until very recently) never been approved to treat Hepatitis B infection. The
FDA did not include any of this information in Viread’s Package Labeling and, therefore, it was considered off-label at the time it was presented and throughout the Class Period.

101. The FDA Briefing Document described Study 903 even though it was incomplete. Under the heading “Plans for Further Development,” the FDA Briefing Document states that Gilead designed Study 903 to evaluate the safety and efficacy of Viread versus Stavudine, another HIV/AIDS drug manufactured by one of Gilead’s competitors. According to the FDA Briefing Document, the forty-eight week data from Study 903 was expected to be available in early 2002. Study 903 was testing Viread as a first-line or initial antiretroviral therapy regimen for treatment “naïve” patients. The success of the study was necessary for Gilead to substantially increase Viread sales by expanding its indication and the patient market of eligible Viread users. Thus, by providing Gilead’s sales and marketing team with Study 903 information in December 2001, Gilead was providing them with off-label information on a study that was not even scheduled to reach completion until early 2002. The sole purpose of providing Study 903 to Gilead’s sales and marketing team was to arm them with data that could be used to sell Viread off-label as a first-line therapy to treatment naïve patients and increase sales. As discussed in more detail below, Defendants’ scheme worked.

102. As with Study 903, Gilead included Study 907, also off-label, in the FDA Briefing Document. Gilead designed Study 907 to evaluate the efficacy of Viread in a large population. Study 907 involved 552 patients who received varying doses of Viread and were deviating from their then-current intake levels of other HIV/AIDS drugs. Gilead designed Study 907 to select patients who had experience with other HIV/AIDS drugs and had a detectable viral load. In the FDA Briefing Document, Gilead described the results of Study 907 as demonstrating that Viread had significant anti-HIV activity.

103. Gilead encouraged the sales and marketing staff to use updates on Study 907 in order to discuss the long-term safety of Viread in patients also taking other HIV/AIDS medications. According to CW1 and CW2, this off-label long-term safety data offered a clear advantage for marketing Viread because many HIV drugs are new to the marketplace and thus lack any long-term data. Accordingly, despite the off-label status of these studies, Defendants encouraged, expected,
and directed Gilead’s sales and marketing staff to use this additional information to promote Viread, in violation of FDA rules and regulations.

104. In addition, CW3 stated that although Viread’s FDA-approved package insert was updated regularly throughout her/his four-year tenure with Gilead, by the time the package insert was updated, the Therapeutic Specialists had moved on to discussing other unapproved data from ongoing studies. For example, if 24-week or 48-week data became FDA approved, the Company’s sales staff would be out promoting and selling Viread based on unapproved 144-week data. CW3 stated this unapproved data from ongoing study results was used to market Viread off-label. When she/he worked as a Therapeutic Specialist, CW3 recalled receiving such unapproved study updates from Studies 902, 903, and 907.

105. Along with the other Confidential Witnesses, CW1 and CW2 witnessed first-hand, along with Defendants Martin, Milligan, and Perry, among others, how the “wink and nod” technique would operate to provide Gilead’s sales and marketing team with off-label information to boost Viread sales and gain an unfair advantage over competitors. For example, at meetings, such as the Arizona National Meeting, the sales and marketing staff would first attend large meetings during which Gilead executives and clinical personnel presented off-label data. Then, the sales and marketing team would break down into smaller groups for additional meetings. It was during these smaller meetings that CW1 and CW2 and other Confidential Witnesses received specific off-label promotional material instructions, as described herein. Typically, the sales and marketing team would then reconvene, where they were told to sell Viread based on what they had been told in the smaller meetings, without any specific mention of the instructions issued. In this manner, Gilead could simply present the off-label material and then quietly instruct, behind closed doors, its sales and marketing people to sell off-label, while continuing to cover itself with a paper trail at the larger meetings. As CW4 recalled, Defendants tried to cover their tracks, knowing that outward directives to promote Viread for off-label use would raise compliance issues.

106. Both CW1 and CW2 recall that at the Arizona National Meeting, Michael Miller ("Miller"), Gilead’s Chief Virologist, made presentations to Gilead’s sales and marketing team
regarding off-label Viread clinical data such as instances of HIV resistance. Among others, Defendants Martin, Milligan, and Perry were in attendance.

107. CW1 and CW2 also recall that, while at the Arizona National Meeting, Fletcher, Gilead’s Director of Marketing, instructed Gilead’s sales team to steer their Viread sales presentations toward off-label information. Among others, Defendants Martin, Perry, Milligan, and Bischofberger were present at this meeting.

108. Defendants knew that their off-label marketing violated FDA rules and regulations. In fact, the FDA concluded that, while attending the December 2001 41st Interscience Conference on Antimicrobial Agents and Chemotherapy in Chicago, Gilead made false and misleading statements about Viread at its promotional exhibit, including statements regarding the risks and efficacy associated with Viread. As explained below, on March 14, 2002, once it learned of Defendants’ misleading promotional campaign, the FDA/DDMAC issued a letter to Defendants condemning their actions (hereinafter the “Untitled FDA Letter”). See Exhibit D attached hereto (a true and correct copy of the Untitled FDA Letter). According to CW1, CW2, and CW5, the statements condemned by the FDA/DDMAC letter were made by Defendant Martin. In fact, according to CW1 and CW2, it was company-wide knowledge that Martin was the cause of the Untitled FDA Letter. CW5 recalled Martin had been promoting Viread as a miracle drug, and that Martin was doing so because Gilead needed to overcome the perception in the medical community that Viread was like Gilead’s previous HIV drugs and would likely cause kidney damage. In essence, Martin was promoting Viread as having a safety profile better than was actually the case in a bid to overcome the negative connotation sometimes associated with Gilead’s HIV therapeutics in the market in the 2001 to 2002 timeframe. Indeed, CW8 also confirmed that Martin would refer to Viread as a miracle product all the time at meetings.

109. On January 30-31, 2002, Gilead held a regional sales and marketing meeting in Chicago (the “January 2002 Mid-West Regional Meeting”) to address slow Viread sales in the Mid-West region. CW1 recalls that during that meeting, DelloStritto, Meyers, Kristin Bennet (“Bennet”), Gilead’s Director of Training, and Mark Bernstein (“Bernstein”), one of Gilead’s Medical Science Liaisons, made it clear to Gilead’s Mid-West Therapeutic Specialists (as had been done at the
Arizona National Meeting) that it was both acceptable and encouraged to violate FDA regulations and market Viread with off-label information without first obtaining a doctor’s request for such information. According to CW1, Gilead echoed that same instruction at several national meetings attended by the Individual Defendants. CW2 attended a similar meeting in Dallas, Texas (the “2002 Dallas Regional Meeting”).

110. At the January 2002 Mid-West Regional Meeting, CW1 recalls Gilead providing updates regarding Viread’s HIV resistance profile and the progression of Studies 902 and 907. Gilead designed Study 902 to test the long-term efficacy of Viread in patients with HIV who were already on other HIV/AIDS medications for at least eight weeks prior to enrollment in the study. The primary objective of Study 907, on the other hand, was to evaluate the safety and efficacy of Viread in a large population.

111. The primary object of Study 902 was to evaluate the long-term safety of three different doses of Viread and to confirm the results of previous efficacy tests. The selection criteria depended upon the amount of the HIV virus present in the patient’s body and what medication the patient was currently taking. The 189 patients in Study 902 had to already be on HIV drug therapy consisting of no more than four active medications for at least eight weeks prior to enrollment. Other requirements related to overall health including renal, hepatic, and hematologic function. Gilead included this study in the FDA Briefing document, but any results that were not approved by the FDA, or any updated results from on-going patient studies, were off-label.

112. Thus, providing Gilead’s sales and marketing staff members with updated, off-label information on Study 902 would permit them to opine on the long-term safety of Viread in patients also taking other HIV/AIDS medications, despite the fact that the FDA had not approved such updated information. According to CW1 and CW2, long-term safety data for any HIV medication is invaluable for marketing such drugs because many HIV drugs are new to the marketplace, creating an inherent lack of long-term data. This perspective was also expressed by several other Confidential Witnesses, including CW5. The ability, or in Gilead’s case, the audacity, to present such data would provide a clear advantage in the marketplace, resulting in increased demand for Viread.
113. Specifically, at the January 2002 Mid-West Regional Meeting, presenters discussed unproven and non-FDA approved theories of how Viread can allegedly remain dormant in a healthy cell, laying in wait for the HIV virus to attack the cell. CW1 recalls that Gilead used this off-label information to give Gilead’s sales and marketing team an advantage over its competition and boost Viread sales. According to CW2, presenters at the 2002 Dallas Regional Meeting discussed the same theoretical and unapproved off-label materials.

114. In addition, prior to the January 2002 Mid-West Regional Meeting, Meyers, Bennet, and DelloStritto specifically instructed CW1 to teach other Gilead Therapeutic Specialists and marketing employees how to successfully market Viread using this off-label information.

115. Specifically, CW1 was told that because she/he was skilled at manipulating potential Viread purchasers into discussing issues which required the disclosure of off-label materials, thus creating openings for discussion of off-label materials, CW1 was selected to teach other salespeople how to lead customers (i.e., physicians and other medical professionals) to these openings. CW1 did as she/he was instructed to do out of fear of losing her/his job.

116. Consequently, in addition to receiving additional off-label information from Gilead executives, CW1 trained no fewer than five other Therapeutic Specialists how to successfully market Viread using off-label information. CW1 recalls that Meyers was present while CW1 instructed other Therapeutic Specialists on how to market off-label. In fact, after all was said and done, Meyers even complimented CW1’s off-label training techniques.

117. On February 11-13, 2002, Gilead held a Field Advisory Committee meeting at the New York offices of Harrison & Star, Gilead’s advertising agency (the “February 2002 Field Advisory Committee Meeting”). CW1 attended this meeting along with a select group of Viread national sales and marketing team members to discuss Viread sales and sales practices with members of Gilead’s executive departments. The attendees included CW1, five other Therapeutic Specialists, Fletcher, Gilead’s Director of Marketing until the summer of 2002, and John Windt (“Windt”), Gilead’s Associate Director of Marketing. CW1 recalls that at the meeting, Fletcher and Windt, as Gilead marketing executives, asked the Therapeutic Specialists how they were using off-label information in the field to promote and sell Viread. In response, the Therapeutic Specialists reported
their experiences utilizing off-label materials to promote Viread and increase their sales of Viread. As a result, CW1 is able to confirm that her/his experiences of marketing Viread with off-label information were the same as Therapeutic Specialists from all regions of the country. Likewise, it is reasonable to infer that other Therapeutic Specialists throughout the United States materially increased their Viread sales as a result of the use of off-label marketing materials. Indeed, as discussed more fully below, 85% to 95% of CW1’s Viread sales were caused by off-label marketing. CW2’s sales were similarly impacted, including during the Class Period. CW1 and CW2 also have stated that as a result of certain “high density” HIV/AIDS population areas, such as New York City, Boston, and Washington D.C., the range of Gilead’s sales of Viread overall that were caused by off-label marketing was between 75% and 95%.

CW6, who sold Viread in the New York City area, stated that “easily 70%” of her/his Viread sales were attributable to off-label sales to treatment naïve patients, and that the Company also encouraged off-label sales to Hepatitis patients. It is therefore reasonable for this Court to infer that between 75% and 95% of all Viread sales during the Class Period were caused by the use of off-label marketing, as discussed more fully below.

118. As at other Gilead meetings, the use of off-label information in the sale and promotion of Viread was specifically discussed and encouraged at the February 2002 Field Advisory Committee Meeting, even in the presence of Gilead senior executives such as Fletcher and Windt. At the time, Fletcher was Gilead’s Director of Marketing and reported to Weisbrich, Gilead’s Vice-President of Sales and Marketing, who, in turn, reported to Inouye and Defendant Martin. Windt reported to Fletcher.

119. On February 20-22, 2002, Gilead held another regional sales and marketing meeting in Chicago (the “February 2002 Mid-West Regional Meeting”). Again, Gilead presenters told the

3 CW1 states that in extremely large United States HIV markets, such as New York City, Boston, and Washington D.C., the percentage of sales caused by off-label marketing was likely to be below 75% because physicians would be more familiar with the existence of AIDS drugs and the higher incidences of HIV make it easier for sales representatives to sell larger quantities of Viread (there was less of a need, and less pressure, to market off-label). As a corollary, CW1 states that in non-HIV intensive markets, the percentage of off-label Viread sales would fall in the 85% to 95% range because it was harder to sell vast quantities of Viread, and thus resort to off-label tactics was necessary to meet sales goals.
sales and marketing staff that it was acceptable and encouraged to promote Viread using off-label information. As at previous Gilead meetings, CW1 was specifically provided with off-label information for Viread, and was encouraged to use that information, in violation of FDA rules and regulations, to make Viread sales. CW1 recalls that during the February 2002 Mid-West Regional Meeting, Miller, Gilead’s Chief Virologist, updated the off-label Viread information. Specifically, Miller discussed Viread’s resistance profile in treatment “experienced” versus treatment “naïve” patients, as part of Gilead’s ongoing, illegal efforts to sell Viread to treatment naïve patients, despite the fact the FDA had not yet approved Viread for such use. At around the same time, CW2 attended a Houston regional meeting wherein Gilead presenters discussed similar substantive materials and gave the same instructions regarding the use of off-label materials.

120. According to CW1 and CW2, at the time of the February 2002 Mid-West Regional Meeting and Houston regional meeting, Gilead was testing Viread’s levels of success in patients already using HIV/AIDS medication (i.e., the experienced indication) and comparing those results to the level of success in patients who had never used HIV/AIDS medication (i.e., the naïve indication). Gilead planned to use this off-label data to expand the indication (use) of Viread into treatment of naïve patients, thus increasing sales, despite the fact that the FDA had approved no data at that time showing that Viread worked as a first-line therapy in treatment naïve patients. Similarly, CW4 stated despite the lack of approval for Viread for treatment naïve HIV patients, marketing and selling Viread to treatment naïve patients was always a key component of the Company’s strategy for Viread. CW6 echoed this experience, stating at least 70% of her/his Viread sales were off-label to treatment naïve patients, and that if Therapeutic Specialists did not sell Viread as a first-line therapy, they would be fired.

121. As described above, one month later the March 14, 2002 Untitled FDA Letter advised Gilead that its representatives’ false and misleading promotional activities violated the Federal Food, Drug, and Cosmetic Act. See Exhibit D.

122. According to the Untitled FDA Letter, Gilead had falsely and misleadingly promoted Viread by stating that it contained “no toxicities,” was “extremely safe,” and was “extremely well-tolerated” despite the fact that its boxed warning and Package Labeling advised to the contrary.
FDA stated that Gilead further violated the Federal Food, Drug, and Cosmetic Act by misrepresenting Viread’s safety profile. Specifically, Gilead minimized Viread’s black boxed warning (part of the Package Labeling) and suggested that its drug was safer than what was demonstrated by scientific evidence. In addition, the FDA stated that Gilead “engaged in false and misleading promotional activities about the efficacy of Viread,” claimed that Viread was “approved for a broad indication” and characterized Viread as a “miracle drug,” even though the FDA had not determined the clinical benefit of Viread in HIV patients.

123. The Untitled FDA Letter ordered Gilead to “immediately cease making such violative statements” and required Gilead to submit a written response to the DDMAC describing its intent and plans to comply with the DDMAC’s directives and identifying the specific date upon which Gilead planned to discontinue its illegal promotional activities.

124. On March 21, 2002, Gilead responded to the Untitled FDA Letter, assuring the DDMAC that its illegal promotional activities would cease (Gilead’s letter stated, in pertinent part, that its letter “constitute[d] Gilead’s commitment to ensure that future violative statements are not made in the promotion of Viread”). As described below, Gilead’s “commitment” did not prevent it from continuing its off label marketing scheme.

B. Defendants Continue to Falsely Promote Viread During 2002, Notwithstanding their FDA Violations

125. Nevertheless, Gilead and the Individual Defendants either specifically directed Gilead’s sales force to engage in the false, misleading, and illegal promotional and marketing activities described by the Confidential Witnesses proscribed by the Untitled FDA Letter, or, at the very least, knew of the ongoing improper and illegal promotional and marketing activities but, with a “wink and a nod,” allowed them to take place, continue, and ratified them. According to CW1, Gilead made no marketing adjustments as a result of the Untitled FDA Letter. Further, both CW1 and CW2 understood (and believed it was company-wide knowledge) that it was Defendant Martin’s comments that resulted in the letter. Similarly, CW8 recalls that Martin referred to Viread as a miracle product and espoused off-label uses for Viread. Indeed, Gilead’s marketing misconduct continued (and, in actuality, increased) over time, including into the Second Quarter 2003.
126. As a result of the specific activities identified, criticized, and rejected in the Untitled FDA Letter, Gilead continued planting the seeds of fraud that ultimately contributed to the artificial inflation of its sales of Viread.

127. The Untitled FDA Letter did not deter Gilead from continuing its campaign of false, improper, and illegal marketing and promotional activities, despite the fact that Gilead assured the DDMAC and the FDA that its illegal activities would cease. Instead, Gilead’s lies continued over time, including into the Second Quarter 2003.

128. According to CW1, in the Second Quarter of 2002, sales representatives were instructed to develop relationships with gastroenterologists in order to off-label market Viread for the treatment of Hepatitis B infection. CW1 received this instruction from her/his regional director. In addition, the off-label use of Viread to treat Hepatitis B infection was discussed at sales meetings by both Gilead’s marketing staff and the Vice President of Sales, Meyers. CW2 confirmed that she/he was instructed to and did attempt to begin to develop relationships with gastroenterologists in order to induce them to prescribe Viread.

129. Similarly, CW4 recalled that Gilead promoted Viread for a Hepatitis B indication. She/he stated that Gilead had the data to support Viread for a Hepatitis B indication, but had not received FDA approval for that indication. Likewise, CW3, CW5, CW6, and CW7 stated Viread was marketed and sold off-label as a treatment for Hepatitis B. As set forth above and in more detail below, CW5 even stated that during April 2003, Gilead presented a slide to its sales force instructing them to market directly to Hepatitis B doctors.

130. During the Class Period, however, Gilead never received FDA approval to sell or market, in any way, Viread as an approved treatment for Hepatitis B infection (regardless of whether the patient was also infected with HIV). In an effort to broaden the indication for Viread, and materially increase sales, Gilead nevertheless funded a small “open-label” patient study of Viread in HIV-1 and Hepatitis B virus co-infected individuals to demonstrate that Viread may work as a treatment option for Hepatitis B infected patients. But, Gilead’s study did not meet the FDA’s requirements for demonstrating the safety or efficacy of a Viread-based therapy for treating Hepatitis B infection – the study only had 20 patients.
131. As a matter of fact, at all relevant times, the FDA had a black box warning concerning the use of Viread to treat Hepatitis B in HIV co-infected patients. The warning stated that use of Viread by co-infected patients is dangerous because there is a risk of severe acute exacerbations of the Hepatitis B infection in patients when Viread is discontinued in such patients. Indeed, HIV positive patients must rotate their usage of antiretroviral drugs, such as Viread, over time to prevent the emergence of “HIV resistance” – a term used to describe the HIV virus’ ability to mutate over time so as to render drugs, such as Viread, ineffective. Thus, according to Viread’s FDA-imposed black box warning, an HIV and Hepatitis B co-infected patient who stops taking Viread due to HIV resistance may, as a result, suffer even more severe, acute liver damage from exacerbations of Hepatitis B infection. Because of these documented problems, Defendants’ off-label marketing potentially and significantly endangered the very patients to whom the drug was being improperly marketed.

132. Despite all of this, CW4 stated that it was common sentiment at Gilead that the Company did not even need to seek FDA approval for Viread as a Hepatitis B treatment option because it would be used for such purposes even without FDA approval. Among other things, CW4 stated this was because of the Company’s marketing of Viread for such off-label uses. CW4 stated that 100% of sales of Viread for a Hepatitis B indication were the result of off-label marketing. CW6 likewise stated the Company’s Medical Science Liaisons were indicating such a dual use for Viread, akin to killing two birds with one stone, to treat Hepatitis B and HIV. She/he recalled that the Company’s Medical Sciences Liaisons accompanied her/him on sales calls all the time because they purportedly had the scientific credibility to discuss off-label uses with physicians during sales presentations. CW6 stated that was why the Company hired medical doctors to be Medical Science Liaisons. She/he believed the Medical Science Liaisons were used to help sell Viread for off-label uses. CW6 stated that this seemed to be the norm at Gilead. Similarly, CW5 stated the Company’s Medical Science Liaisons were used as an off-label marketing tool and often operated in a sales capacity during CW5’s tenure at Gilead. CW5 recalled that Bill Guyer (“Guyer”) was a Gilead Medical Science Liaison who regularly acted in a sales role and disseminated off-label information
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about Viread. CW5 stated that in approximately 2003, Guyer presented data to the incoming HIV Therapeutic Specialists about Viread's use as a treatment for Hepatitis B co-infected patients.

133. On April 17-18, 2002, Gilead held a regional sales and marketing meeting in Chicago to update its Mid-West sales force with additional off-label information. CW1 attended this meeting, and specifically recalls Gilead presenters once again providing the Mid-West sales and marketing team with updated off-label Viread information and encouraging them to use the materials to illegally promote Viread.

134. On May 6, 2002, CW1 attended a meeting of Gilead’s Field Advisory Committee in New York (the “May 2002 Field Advisory Committee Meeting”). Fletcher and Inouye also attended this meeting.

135. During the May 2002 Field Advisory Committee Meeting, CW1, along with a handful of other Therapeutic Specialists from around the country, described to Gilead’s marketing officers and executives, including Inouye and Fletcher, how they were promoting Viread in all regions. Specifically, CW1 recalls discussions regarding how the sales and marketing staff was promoting Viread with off-label information. In fact, the attendees specifically discussed off-label clinical information that recently had been provided to physicians at a conference in Seattle, Washington. Again, CW1 and the other members of the Field Advisory Committee were updated with additional off-label information that Gilead would be presenting at an upcoming July 7-12, 2002, international AIDS/HIV conference in Barcelona, Spain. The recurring discussions between and among Therapeutic Specialists during Field Marketing Advisory Committee meetings are a powerful backdrop for CW1’s estimate that 75% to 95% of all Viread sales were caused by off-label marketing as well as CW2’s estimate that 85% to 90% of all Viread sales during the Class Period were a direct result of off-label marketing and CW6’s estimate that at least 70% of her/his Viread sales were off-label. These facts provide additional support for the Court drawing an inference that, like CW1, CW2, and CW6, all Gilead sales people materially increased sales of Viread as a direct result of off-label marketing.

136. On May 14-17, 2002, Gilead held a sales and marketing meeting in Los Angeles, California for four sales regions of the country including Chicago, Dallas, Los Angeles, and San
Francisco (the "2002 Los Angeles Regional Meeting"). At the meeting, Gilead presenters provided
the sales and marketing staff from these four regions with additional off-label information to use in
the promotion and sale of Viread and off-label clinical and theoretical information that was going to
be presented at the upcoming July 2002 international HIV/AIDS conference in Barcelona, Spain.
CW1 and CW2 attended the meeting and recall that Defendants Meyers, Perry, and Martin were
present when presenters directed Gilead's sales and marketing people to use off-label information.

137. Specifically, CW1 recalls discussions at the 2002 Los Angeles Regional Meeting
regarding Viread's efficacy in the treatment of Hepatitis B infection. CW1 and the other attendees
were instructed to market Viread for the treatment of HIV and Hepatitis B infection in order to boost
sales, despite the fact that Viread was only approved for HIV.

138. Thus, as with all of its other meetings, at the 2002 Los Angeles Regional Meeting
Gilead continued to inundate its sales and marketing staff with off-label information, while
encouraging, expecting, and directing them to use it to promote Viread in violation of FDA rules and
regulations. According to CW1 and CW2, the practice of providing off-label materials to boost sales
began with and ran to the highest levels of Gilead's hierarchy, including Defendants Martin,
Bischofberger, Perry, Milligan, and Lee, among others. CW3, CW4, and CW5, among others, also
stated the Company's practice of providing its sales force with off-label materials ran from the top-
down at Gilead.

139. On July 15, 2002, CW1 raised concerns with DelloStritto in Chicago, Illinois
regarding the use of off-label information. CW1 recalls that DelloStritto wanted more sales from the
Mid-West territory and told CW1 that if CW1 used more off-label data, CW1 would get more sales.

140. Gilead's senior management continuously and repeatedly instructed Gilead's sales
force to utilize off-label materials in order to sell greater quantities of Viread. For example, in mid-
2002, Bill Strong ("Strong"), Gilead's Region Trainer for the Dallas Region, accompanied CW2 on a
number of sales calls in order to provide CW2 with "additional training" if necessary. After
observing CW2's performance, Strong attempted to train CW2 to increase his focus on and
utilization of off-label materials to more effectively market Viread. Among the off-label materials
Strong emphasized were materials regarding Viread's efficacy, safety risks, and dosages. In
response, CW2 informed Strong that he believed it was improper for CW2 to follow Strong's directive and utilize off-label materials to market Viread. Nevertheless, CW2 was forced to utilize off-label materials in order to make sales and keep her/his job.

141. On July 15, 2002, Kaiser and Robert Wallace ("Wallace"), one of Gilead's Medical Science Liaisons, summoned CW2 to a meeting at the Atlanta airport Westin Hotel. During this meeting, Kaiser and Wallace instructed CW2 that, instead of selling Viread using the materials in the Package Labeling, he or she should sell Viread using the "theory of HIV" and the "theories behind the benefits of using Viread," despite the fact that none of these "theories" were approved by the FDA and that many were unsupported by scientific studies. CW2 again expressed her/his reluctance to use off-label materials to market Viread.

142. In fact, as a result of her/his meeting with Kaiser and Wallace, Meyers summoned CW2 to a meeting at the Bellagio Hotel coffee shop in Las Vegas, Nevada (CW2 and Meyers were both in Las Vegas for Gilead's September 9-13, 2002 national meeting (the "Las Vegas National Meeting")), to discuss her/his position on off-label marketing. During this meeting, Meyers expressed his exasperation at CW2's refusal to maximize her/his use of Viread off-label marketing materials. Meyers told CW2 that if CW2 failed to fit the mold of a Gilead Therapeutic Specialist, CW2 would not be able to make her/his sales numbers. Despite CW2's continued reluctance to use off-label materials to market Viread, CW2 assured Meyers that she/he could do her/his job and work with both Kaiser and Wallace. In short, CW2 was given no choice but to follow Defendants' directive and utilize off-label marketing materials to sell Viread. As set forth below, despite CW2's reservations, CW2 did off-label market and CW2 states that 85% to 95% of her/his sales, including those sales during the Class Period, were caused by CW2's use of off-label marketing tactics.

143. While attending the Las Vegas National Meeting, CW1 and CW2 recall that Inouye and Defendants Milligan, Perry, Bischofberger, and Martin were also present. Once again, Gilead's presenters provided the marketing and sales team with substantial amounts of off-label information to use to sell Viread by differentiating it from the competition. Specifically, Gilead's presenters discussed clinical data, not yet approved by the FDA, which had been presented at the July 2002
international HIV/AIDS conference in Barcelona, Spain, as well as other new theories on Viread’s resistance profile.

144. CW1 and CW2 believe that without making improper, off-label distinctions as part of its standard sales practice, Gilead would not have had such rapid success in the promotion of Viread.

145. On October 10-11, 2002, CW1 attended another meeting of the Field Advisory Committee at Gilead’s headquarters in Foster City, California. Meyers, Kelly Seither, Gilead’s Associate Director of Marketing, and Inouye, as well as other Therapeutic Specialists from around the country attended the meeting. At the meeting, Gilead presenters provided CW1 and other Therapeutic Specialists with updated information regarding Study 903, which had just reached the three-year mark. The presenters told them how to push Viread with additional results from Study 903, results not found in the Package Labeling and not approved by the FDA. The incomplete Study 903, testing Viread as a first-line therapy in treatment naïve patients, was again being used by Defendants to increase Viread sales through off-label marketing.

146. On October 17, 2002, CW1 attended a regional meeting of the Mid-West Viread sales and marketing team in Chicago, Illinois. As at other national and regional meetings, Gilead presenters provided CW1 and the other members of the sales team with off-label information and encouraged them to use such information to sell Viread. Likewise, CW2 attended a regional meeting in Dallas and was given the same directives.

147. On November 1, 2002, CW1 attended a national liver disease meeting in Boston, Massachusetts. Numerous representatives from Gilead attended the meeting, including Defendants Martin and Perry, and Meyers. Because Viread was not approved to treat Hepatitis B infection, the only reason Gilead executives would have attended this meeting was to make contact with, and attempt to influence, liver specialists to prescribe Viread. During the meeting, on November 2, 2002, CW1 met with Meyers to discuss the off-label marketing of Viread, and the prevalence of Gilead’s false, misleading, and improper sales practices. Rather than alleviate CW1’s concerns, Meyers instructed CW1 to use every piece of available off-label information to promote Viread, to sell Viread with the information presented at the national and regional meetings, and to do as CW1 was told.
148. After working as a Therapeutic Specialist, CW3 was promoted to the position of Manager of Training in approximately late 2002. As a Trainer, CW3's role was to write-up materials for use by the Company's sales force in their presentations to doctors that contained both information about Viread that was approved by the FDA and unapproved information from recent conferences and ongoing studies. For example, CW3 was tasked with getting materials updated and distributed to regional trainers.

149. CW3 stated Gilead's training department, however, was being used to deliver marketing's message. Because the Company's marketing department could not overtly tell the sales force to sell off-label, Defendants' sales strategy for Viread entailed the incorporation of unapproved study data being placed in training materials that were then used by Therapeutic Specialists in sales calls in their respective territories. In other words, Defendants used the Company's official training department and materials to deliver off-label information to Gilead's sales force — putting the Company's official stamp of approval on the use of off-label information to illegally sell Viread. In basic terms, CW3 stated it was the Company's strategy to provide off-label materials to sales team members for promotional purposes.

150. CW3 noted the Gilead HIV Therapeutic Specialist training materials, including those throughout the Class Period, contained a great deal of off-label information, and that these training materials were provided to the Therapeutic Specialists not just to keep them apprised of recent events and results of studies in the industry, but also specifically for use as talking points with the doctors on which they called to sell Viread. As an example, CW3 pointed to posters from conferences that were reduced in size, color-copied, and distributed to the Therapeutic Specialists for use in their sales calls. For instance, posters presented at the Interscience Conference on Retroviruses and Opportunistic Infections ("CROI") regarding the most recent study results for Viread were distributed as part of the marketing materials provided to the Gilead sales team for Viread. These documents were commonly known to the sales team members as "backgrounders." As set forth above, several other Confidential Witnesses, such as CW5, confirmed off-label materials were provided to the sales force through training materials, binders, and "poster books."
151. In addition, CW3 recalled that Meyers, Gilead’s Vice President of U.S. Sales, directed CW3 to write training materials for Viread’s sales force that contained bullet points layered with both FDA-approved and unapproved, recently-released study data. At Meyers’ direction, CW3 prepared “abstracts” on the results of recent studies of Viread for off-label indications and documents that contained bullet points that highlighted potential uses of Viread — including for off-label purposes. The inclusion of unapproved data in the Therapeutic Specialist training materials and talking points was concerning to CW3 because the Therapeutic Specialists were being encouraged to engage their existing and potential clients in off-label discussion regarding Viread using the information contained in the documents they received. She/he recalled the unapproved data basically expounded on the approved studies and widened the indications for Viread during the Class Period.

152. Similarly, the sales scripts CW3 prepared were presented and provided to Therapeutic Specialists at national and regional sales meetings. While CW3 drafted the training materials containing off-label data that were used by the Therapeutic Specialists to market and sell Viread for off-label indications during the Class Period, CW3 did not present such data. Rather, when the results of new studies were presented to the sales force, the presentations were made by the “Clinical Science” staff. For example, CW3 stated Defendant Bischofberger made presentations about the study data to the sales organization, including providing details on some of the information that CW3 incorporated in the training materials. Also, Chief Virologist Miller was Gilead’s “resistance” specialist, and made presentations to the sales force regarding off-label study data related to resistance issues, such as the issue with the “K65R mutation.”

153. On top of the national and regional meetings discussed herein and below, CW3 states there were internal Gilead weekly meetings from at least late 2002 until at least January 2005 – throughout the Class Period. Held in conference rooms at the Company’s Foster City, California headquarters, the meetings were conducted to discuss the provision of off-label materials to HIV sales force. These meetings were attended by marketing and training department heads, sales directors, CW3, and Meyers was brought in at the end of each meeting.
154. At these weekly meetings, there was a debate about whether to continue to provide off-label data to the Therapeutic Specialists, and this represented a point of contention within the Company in the period leading up to and throughout the Class Period. CW3 stated there were essentially two disparate opinions about the distribution of off-label materials to the sales force, which included those who thought the sales force should receive no off-label materials and those who believed it necessary to provide the sales force with off-label data and information. CW3 stated the Company’s “Clinical Staff” did not want the sales representatives to have any off-label documentation. By contrast, the marketing and sales departments and personnel desired that the Therapeutic Specialists received regular updates about the status of studies on Viread and updates on findings from such studies that could and were used in discussions with practitioners in violation of FDA rules. CW3 stated Meyers supported the latter notion – namely that Therapeutic Specialists should continue to receive off-label marketing materials, and Meyers directed the provision of such materials be done through the training department. Thus, the systematic use of illegal, off-label marketing at Gilead was not the by-product of rogue salespeople or a handful of careless Therapeutic Specialists who did not know the difference between right and wrong. Rather, the decision to provide the sales force with off-label information for illegal marketing and sales activities was deliberate, came from the highest levels within the Company, and was uniformly applied on a Company-wide basis through training materials given to the entire Viread sales staff.

155. For example, the documents included in the training binders that Gilead and CW3 created included the Viread package inserts, package inserts for competing drugs, tables with side-by-side comparisons of each, and other “approved training material,” and off-label materials. CW3 stated that before her/his promotion in late 2002, there were some disclaimers on the documents submitted to the sales force indicating they were off-label materials not to be used for promotional purposes, but this was not the norm. As such, CW3 stated these materials were used to sell and promote Viread off-label by Therapeutic Specialists.

156. By the time CW3 was promoted in late 2002, internal discussions within the Company regarding the distribution of off-label marketing materials to the HIV Therapeutic Specialists had reached the point where senior management acknowledged it was inappropriate for
the Company’s marketing department to disseminate such information to the sales force. Thus, the
training department became the sacrificial lamb through which Defendants would accomplish their
fraudulent scheme of off-label marketing. CW3 stated that she/he became part of the “wink and
nod” process of supplying the Therapeutic Specialists with the information they utilized to market
and sell Viread off-label.

157. Despite being tapped with delivering Defendants’ off-label message to the sales force
through training materials, CW3 tried in vain to implement a certain standard of ethics. For
example, beginning in 2003, she/he implemented a practice of watermarking documents that were
distributed by the training organization. The watermarks were initially small and on the side or
margins of the documents – which enabled them to be easily copied with the watermarking removed.
Throughout the remainder of her/his tenure, however, CW3 changed her/his practices and made the
watermarks larger and posted diagonally across the entire page. The watermarks read “not for
promotional use.”

158. CW3’s efforts to implement controls to prevent illegal off-label marketing were met
with stern objections and often circumvented at high-ranking levels without consequence. Meyers
and the sales managers objected to CW3’s efforts to implement such controls. Indeed, members of
the sales team were able to get from other sources clean copies of the same documents watermarked
by CW3. CW3 stated the Company’s actions appeared to be a deliberate effort to circumvent any
limitations on the provision of off-label information to Therapeutic Specialists for sales and
marketing purposes. For example, CW3 knew that the Therapeutic Specialists had copies of non-
watermarked documents because the Regional Trainers informed CW3 that their subordinate sales
personnel already had non-watermarked copies of the documents. CW3 believed the Therapeutic
Specialists were using the non-watermarked copies of the documents in discussions with HIV
practitioners and stated there were no processes in place at Gilead during the Class Period to prevent
the use of such non-watermarked materials for selling purposes. For example, CW6 stated that
although many off-label materials were stamped “For Educational Purposes,” those designations
could easily be covered up when reproducing the document and that any such designation “was a
joke.” CW3 stated she/he implemented the attempted internal control of watermarking on her/his
own initiative because she/he was very uncomfortable to be in the role of Training Manager while being asked by Meyers to execute the Company’s off-label marketing strategy for Viread through the dissemination of off-label data to the sales team.

159. CW5 stated that although the training department watermarked some of the promotional materials as being “not-for-promotional” use, this attempted internal control was circumvented throughout the Class Period. In particular, CW5 stated there were “poster books” of study abstracts and updates pertaining to Viread that Gilead prepared for circulation at major medical conferences. The “poster books” consisted of spiral bound notebooks containing Viread study updates, which were approved by the Company’s Medical Affair’s team and Statisticians. These “poster books” were distributed to physicians at the conferences and did not contain any markings indicating the documents were confidential or that they should not be used for promotional purposes. CW5 stated the Gilead Regional Directors and Therapeutic Specialists had access to these “poster books” and used them to promote Viread for off-label indications. As such, even though CW3 and CW5 attempted to implement certain internal controls to minimize off-label marketing (such as watermarking), these controls were easily and often circumvented because of the Therapeutic Specialists’ ability to obtain clean copies of the same documents.

160. More specifically, CW5 stated that the “poster books” used by the Therapeutic Specialists during the Class Period contained abstracts from Study 903, such as week-96 data from Study 903. CW5 stated Therapeutic Specialists were trained by Gilead on how to use the data in the “poster books.” According to CW5, the “good” sales representatives at Gilead during the Class Period had the Study 903 data (i.e., off-label data on use of Gilead in treatment naïve HIV patients), and knew how to use it.

161. CW5 stated the Therapeutic Specialists utilized the “poster books” in role-playing as part of Gilead’s training process. In this regard, CW5 stated that the HIV Therapeutic Specialists were not only provided with the requisite materials to market Viread off-label during the Class Period, but were also training on how to use the off-label study data in discussions with doctors. As an example, CW5 noted the HIV sales force was trained to ask leading questions, or to ask questions that would prompt the physicians on which they were calling to ask about off-label indications for
Viread. One such type of lead question that the HIV Therapeutic Specialists were trained to ask physicians was, “What kind of things do you do for your patients who are infected with Hepatitis B?” This question typically prompted the physician to ask about whether Viread could be used to treat Hepatitis B. CW5 stated the Viread sales force would then answer the physician’s question using off-label data showing Viread to be an effective treatment for Hepatitis B.

162. CW3 reiterated that at Gilead, there was an obvious, covert off-label marketing strategy, whereby the Therapeutic Specialists were able to use off-label materials to promote and sell Viread. The emphasis at Gilead was on attaining sales goals, even though attainment of those goals meant the Therapeutic Specialists would engage in off-label marketing of the drug.

163. For example, CW3 stated there was an initial push, following the launch of Viread in 2001, to market Viread to the practitioners with an experienced patient base. These practitioners were an easy sell for the Gilead sales force. Sales of Viread began to level off, however, around the time CW3 was promoted to the Manager of Training in late 2002, and in the months prior to the Class Period. She/he stated that towards the end of 2002, the Company’s internal sales goals became unrealistic, and in order for the Company’s sales force to meet the increasingly unrealistic goals, the Therapeutic Specialists had to have a broader reach. This broader reach meant expanding promotional activities beyond the easy sales and reaching beyond the experienced patient market to off-label areas.

C. Defendants’ False Promotional Practices Continue in 2003, and into the Class Period

164. On February 17, 2003, Gilead held a national meeting in Orlando, Florida. While at the meeting, CW1 and CW2 attended presentations concerning off-label information on Study 903 and Study 907 by Meredith, Gilead’s Marketing Director, and Linda Cherry (“Cherry”), Gilead’s Associate Marketing Manager. The information was presented to the sales staff in the form of key points from the off-label studies. Presenters Meredith and Cherry instructed CW1, CW2, and other members of the sales and marketing team to utilize the off-label key points to push their sales of Viread. CW1 recalled the instructions being less overt than in the past, but that when the sales teams met in smaller groups, the off-label marketing instructions were much more direct.
165. According to CW1 and CW2, Defendants Martin, Milligan, Bischofberger, Lee, and Perry, among others, were in the room when these instructions were given.

166. As described above, CW5 recalled that in the months prior to April 2003, Gilead had been losing ground on Viread sales. As such, a “re-launch” of Viread was necessary, and a planned, executed off-label strategy was required to make up this lost ground. As detailed in the April 2003 slide in question, at least part of the off-label marketing strategy for Viread entailed marketing Viread for patients co-infected with Hepatitis B, including promoting Viread as a treatment for Hepatitis B to gastroenterologists who treated HIV-infected patients. This strategy was facilitated by the Gilead Sales Analytics team, including gastroenterologists on the marketing lists for the Company’s HIV Therapeutic Specialists. CW5 recalled that Dr. Cazen was one particular gastroenterologist in the San Francisco, California area who treated co-infected patients and to whom Gilead marketed Viread as a treatment for Hepatitis B during the Class Period.

167. In May 2003, CW2 was required to attend a meeting with Packard, one of Gilead’s regional directors, at the Westin Hotel in downtown Atlanta. During this meeting, Packard criticized CW2 for his or her continued refusal to maximize his or her utilization of off-label materials to sell Viread. Thus, throughout CW2’s career at Gilead, CW2 experienced first-hand Gilead’s constant pressure to participate in its scheme to increase Viread sales through off-label marketing tactics.

168. CW3 recalled that in early 2003, the Company almost doubled its Viread sales force, adding at least 40 new Therapeutic Specialists in approximately mid-2003, and divided the eight existing sales territories into 12 regions. Further, there became a very obvious use of Viread in treatment naïve HIV patients. Although the increase in the number of Therapeutic Specialists should have increased sales, it should not have led to a change in the way Viread was being prescribed – not without off-label marketing. CW3 stated that beginning in the first half of 2003, there was a dramatic switch in numbers – or a notable change in the way Viread was being prescribed. CW3 stated that sales skyrocketed as a result of increased prescriptions to the treatment naïve patient market – for which Viread was not approved at the time. CW3 stated the treatment naïve market was extremely important for Gilead, but was difficult to penetrate for several reasons. First, Gilead did not have approval for a treatment naïve indication until late 2003. Second, practitioners would
typically want to test out Viread in experienced patients before prescribing it to treatment naïve patients. To accomplish this, Therapeutic Specialists marketed Viread as having a better safety profile than was indicated on the Package Labeling and marketed it as being as having no side effects.

169. CW3 estimated that prior to and during the Class Period, the segmentation of HIV patients was approximately 60% experienced patients, 30% naïve patients, and 10% salvage patients. Although the experienced segment of the market was larger, it was a more limited market niche, and represented easy sales for Gilead because experienced patients often developed mutations and resistance profiles that required practitioners to try other treatments. In other words, experienced patients were more likely to switch from using Viread to another drug in a shorter period of time than treatment naïve patients. The naïve market niche was more difficult to penetrate, but very important to Gilead and the growth of sales and market share pertaining to Viread. CW6 confirmed Viread sales representatives sold the drug as a first line therapy to treatment naïve patients “all the time” and that if they did not do so, they would be fired.

170. Penetrating the treatment naïve market is where Defendants’ off-label marketing scheme came into play, and the Company used its training department as the sacrificial lamb to get more off-label information to the sales representatives about off-label indications for Viread, including favorable study results regarding the naïve indication. Moreover, despite CW3’s attempts to implement her/his own controls in the distribution of off-label training materials, those controls faced stiff objections and were circumvented. Thus, off-label sales to the treatment naïve market skyrocketed. Indeed, CW6 was provided with off-label promotional materials to push Viread sales to the treatment naïve market, and estimated that at least 70% of her/his Viread sales were for off-label, treatment naïve use. CW6 stated the Company was pushing sales to treatment naïve patients because if Gilead got Viread to a treatment naïve patient, that patient was likely to take Viread for a very long time. In other words, access to the off-label treatment naïve market meant not only increased prescriptions, but increased renewals of those prescriptions for a period of many, many years.
171. Similarly, CW5 recalled there was definitely a drive within the Company to get
doctors to prescribe Viread to treatment naïve HIV patients, prior to its approval for such use, during
the Class Period. CW5 stated this was done as a means to rejuvenate the growth in sales of Viread.
For example, CW5 stated the entire Therapeutic Specialist team was aware that the Study 903 data
(on Viread’s use in treatment naïve patients) was coming down the pipeline. CW5 stated that Gilead
had to expand the scope of indications to include promoting Viread for off-label purposes in order to
continue to gain market share and increase sales during the Class Period.

172. On June 23-27, 2003, CW2 attended a Gilead national meeting in San Francisco (the
“San Francisco National Meeting”) during which Gilead continued to instruct its sales staff on how
to effectively use off-label materials to market Viread. Specifically, Gilead presenters instructed
Gilead’s sales staff, including CW2, on how to overcome the following four objections that potential
customers raise regarding Viread: (1) “So Viread is now causing renal problems . . . I knew this
would happen”; (2) “I am concerned about my NRTI options when my patients fail Viread”; (3) “I
don’t believe in qd regimens”; and (4) “My patients tolerate Zerit and I don’t see the lipoatrophy
develop in them.”

173. In order to combat these objections, during the San Francisco National Meeting,
Gilead provided its sales staff, including CW2, with a memorandum which included off-label talking
points to be utilized in order to convince potential customers to look past these objections and
purchase Viread (the “Off-Label Talking Points”). See Exhibit E attached hereto (a true and correct
copy of the Off-Label Talking Points).

174. On CW2’s information and belief, Meyers and Rich were present in the room at the
San Francisco National Meeting when Gilead’s presenters provided the sales staff, including CW2,
with the Off-Label Talking Points. Further, on CW2’s information and belief, Inouye and
Defendants Martin, Milligan, Perry, and Lee, were present at the meeting (which was attended by all
Medical Science Liaisons, Regional Directors, and National Account Managers) although they were
not physically present in the room for the distribution of the Off-Label Talking Points.

175. CW2’s knowledge and belief of Defendants’ scienter is further supported by her/his
knowledge of Gilead’s standard protocol regarding preparation for regional and national meetings.
176. According to CW2, it was standard practice for all of Gilead's Regional Directors, prior to each national and regional meeting, to travel to Gilead's corporate headquarters in Foster City, California to meet with Gilead's senior management. During these meetings, which included, at various times, Defendants Martin and Perry, as well as Meyers, Weisbrich, Rich, and Helen Harris, the Regional Director of the Mid-Atlantic Region, Gilead's senior management would instruct Gilead's Regional Directors on what training was to be provided to Gilead's sales staff, including training on the use of off-label marketing materials.

177. Just like it did on a daily basis ever since Viread's approval in October 2001, as well as in December 2001, in the Second Quarter 2003 Gilead continued to minimize important risk information (including failing to disclose potentially fatal risks) and broaden the indication for Viread. This time, Gilead's improper and illegal campaign of lies led the FDA, through the DDMAC, to issue a warning letter.

178. On March 31-April 2, 2003, during the 15th National HIV/AIDS Update Conference in Miami, Florida, Gilead made additional off-label oral representations concerning Viread -- this time to an FDA employee who was monitoring sales practices -- which minimized important risk information (including potentially fatal risks) and broadened the indication for Viread. As a result, on July 29, 2003, Second Quarter 2003 – the beginning of the Class Period – the FDA issued a warning letter to Gilead (the "FDA Warning Letter"). See Exhibit F attached hereto (a true and correct copy of the FDA Warning Letter).

179. According to the FDA's website and the FDA's Regulatory Procedures Manual, warning letters such as this are written communications from the FDA’s DDMAC, to a company notifying the company that the DDMAC considers one or more promotional pieces or practices to be illegal. If the company does not take appropriate and prompt action to correct the violation, as requested in the warning letter, there may be further enforcement actions without further notice. Warning letters are issued by the DDMAC Division Director and receive concurrence from appropriate officials in the Center for Drug Evaluation and Research. A warning letter is much more serious than an untitled letter.
180. The FDA Warning Letter, issued during the Class Period and addressed to defendant Martin, stated that Gilead's illegal acts were "particularly troubling because the more than 1,500 attendees of [the 15th National HIV/AIDS Update Conference] included social workers, AIDS educators, and patients with HIV/AIDS."

181. As stated in the FDA Warning Letter, Gilead's lies were so outrageous that Gilead had created a new "intended use" for Viread, causing it to be misbranded.

182. According to the FDA Warning Letter, Gilead's repeated omissions and misrepresentations regarding Viread caused "significant public health and safety concerns," and led the FDA to require Gilead to respond with a plan to address the "repetitive promotional activities."

183. Defendants either specifically directed Gilead's sales force to engage in the fraudulent, misleading, and illegal promotional and marketing activities identified in the FDA Warning Letter or, at the very least, knew of the improper and illegal promotional and marketing activities but allowed them to take place.

184. In response to Gilead's repeated misconduct, the DDMAC requested in the FDA Warning Letter that Gilead take "action to disseminate accurate and complete information to the audience(s)" that received the misleading Viread promotional information. Thus, on November 7, 2003, Defendant Martin purported to write an open letter to all attendees of the 15th National HIV/AIDS Update Conference in Miami, Florida, entitled "IMPORTANT CORRECTION OF DRUG INFORMATION" (the "Correction Letter"). See Exhibit G attached hereto (a true and correct copy of the Correction Letter).

185. In the Correction Letter, Defendant Martin stated that the DDMAC instructed Gilead to contact conference attendees (there were over 1,500) because of misleading oral statements Gilead made in the promotion of Viread. The purpose of the Correction Letter was to provide "accurate information about Viread and [to correct] certain information as cited in the Warning Letter."

186. More specifically and contrary to what Gilead represented at the conference, Defendant Martin described how Viread: (1) does indeed have serious, potentially fatal, side effects; (2) is a "nucleotide," but belongs to the same class of drugs as "nucleosides"; (3) is a nucleotide, but that fact does not make it better or safer than other HIV drugs and does not make it more potent with
fewer side effects (an important clinical distinction the FDA determined Gilead failed to make); (4) is approved only for use in combination with other anti-HIV medicines to treat people with HIV-1 infection; and (5) has not been proven to lower cholesterol levels.

187. As indicated by the Confidential Witnesses, Defendant Martin and the other Defendants knew, prior to the Correction Letter, that Gilead’s sales and marketing team was consistently instructed and trained to market Viread with off-label information that, among other things, misrepresented Viread’s safety profile by minimizing critical risk information, illegally promoted Viread as a first-line therapy for treatment naive patients, and illegally promoted Viread as a treatment for Hepatitis B-infected patients.

188. As a result of the activities identified, criticized, and rejected in the FDA Warning Letter as well as the consistent promotion of Viread by way of off-label information, Gilead caused a substantial increase in its sales of Viread during Second Quarter 2003. CW1 and CW2 state that 75% to 95% of Viread sales, including sales during the Class period, were caused by off-label marketing.

189. According to CW2 and CW5, the FDA Warning Letter was a result of comments made by Augustino “Tino” Quintero, one of Gilead’s Therapeutic Specialists, at the 15th National HIV/AIDS Update Conference in Miami, Florida. In accordance with Gilead’s sales force training, Quintero utilized off-label information when responding to inquiries regarding Viread. Unfortunately for Gilead, the questions Quintero was asked were posed by FDA representatives who were attending the conference specifically to monitor Gilead’s sales and marketing tactics.

190. Amazingly, but not surprisingly, Gilead did not fire Quintero for making the off-label comments that he was taught to make by Gilead. Instead, subsequent to making those comments and subsequent to the issuance of the FDA Warning Letter, Gilead rewarded Quintero with membership in Gilead’s “President’s Club,” a distinction reserved for Gilead’s top sales producers. According to CW5, Quintero remains employed by Gilead, which would be impossible at other companies where off-label sales are grounds for termination.

191. CW1’s and CW2’s accounts of the numerous meetings and presentations attended by them, including national and regional meetings, provide a telling and disturbing snapshot of Gilead’s
sales practices and culture. All of the Confidential Witnesses' collective accounts of the significant
details of Gilead's systematic presentation of off-label information to market Viread, and the
stunning impact the use of that off-label information had on Viread sales, are virtually identical. At
regional meetings, Gilead encouraged CW1, CW2, and other sales team members to aggressively
sell Viread with off-label information. At national meetings, Gilead instructed its entire Viread sales
force to market Viread with off-label studies and information that were deliberately provided by the
Company's training department, as described by CW3 and CW5. Indeed, CW1 and CW2's detailed
accounts of the national meetings strongly suggest that their experiences at Gilead were neither
atypical nor uncommon; rather, their experiences were the norm. Gilead's sales people were
required to and did utilize off-label marketing materials to sell Viread. Both CW1 and CW2
discussed the use of off-label marketing with other members of Gilead's sales force who confirmed
their use of off-label information and the fact that their use of such information stimulated sales. It
is, therefore, reasonable to infer that 75% to 95% of Viread sales during the Class Period were
caused by off-label marketing as the impact is equally applicable to other Gilead salespeople as it is
to CW1, CW2, and CW6.

192. At the various meetings described above, Gilead also provided its Viread sales force,
including the Confidential Witnesses described herein, with numerous slides, posters, and
presentation materials that came directly from the Company's training department. These posters
and presentations detailed the off-label clinical information presented at a given meeting. Typically,
pharmaceutical manufacturers stamp all such materials with a designation that they should not be
used in sales and marketing presentations — that they contain clinical research not approved by the
FDA. Defendants did not do this and circumvented CW3's attempts to do this precisely because
they intended that these off-label materials would be used to market Viread. As described by CW6,
any attempt to restrict use of these off-label materials was a "joke." CW6 also had access to
PowerPoint presentations from the Company's Medical Science Liaisons, and the slides could be
and were used in sales calls. Based on repeated directives to use off-label data to sell Viread, CW1
recalls that there was not one day that went by during the course of CW1's selling of Viread that
CW1 was not utilizing data that was not yet approved by the FDA.
193. According to CW1 and CW2, often the posters would be distributed with an accompanying memorandum describing them as off-label; however, the posters themselves would completely lack any off-label designation. CW6 recalled that if the off-label materials did have any special designation, it was stamped on the bottom or in the margins, such that the designations could easily be eliminated during photocopying. This would enable Gilead’s sales and marketing team members to use the information in sales presentations without the customer realizing that he or she was seeing off-label information. Therefore, as it did in national and regional meetings, Gilead was able to continue its “wink and nod” tactics even with off-label posters. As recounted by CW3, the Company’s training department was tasked with disseminating off-label materials to the sales force.

D. Defendants’ Off-Label Promotion Increased Sales of Viread

194. At all times relevant to the Class Period, Defendants’ continued use of off-label marketing of Viread worked, causing physicians to prescribe more Viread. In addition, Defendants’ off-label marketing caused physicians to prescribe Viread for purposes other than those approved by the FDA. Thus, off-label marketing had its intended impact – Defendants significantly increased Viread sales.

195. CW3 stated there was definitely a “wink and nod” strategy to promote Viread off-label both before and during the Class Period. This strategy was driven by the desire for increased growth in the sales of Viread, as well as the premise that the HIV market was centered on a “dynamic disease,” for which new data was regularly emerging. And, as CW3 confirmed, Gilead’s strategy to market for off-label indications followed the tone from the top, as set by Defendant Martin, who routinely spoke about Viread off-label. Through following Martin’s lead and observing Martin’s off-label promotion of Viread, the Therapeutic Specialists learned that such behavior was the acceptable and expected practice.

196. In the Washington state region to which CW3 was assigned when she/he was a Therapeutic Specialist, Martin often spoke to doctors with practices that entailed the treatment of 200 to 500 HIV patients and key opinion leaders to promote Viread for off-label indications. CW3 explained there were doctors who were heads of large HIV departments or who led regional medical centers, and who typically would not agree to see a Therapeutic Specialist. These more high profile
HIV practitioners, however, would allow appointments from a Gilead Medical Science Liaison or Martin. When a Medical Science Liaison or Martin visited the more high profile HIV practitioners, the nature of the visit was typically a sales call and CW3 stated that off-label information was often disseminated in such sales calls.

197. While Martin’s observed off-label promotion of Viread occurred prior to the start of the Class Period, CW3 confirmed the Company’s off-label promotion of Viread continued into the Class Period. As set forth above, during the Class Period, CW3 was directed to write-up and develop training materials for the sales force that included off-label details regarding Viread. CW3 received a clear message from Meyers to include such information in the training materials for incumbent and incoming Therapeutic Specialists.

198. According to CW1, approximately 50-60% of HIV patients were included in an initial therapy group of patients who were using an HIV drug regimen for the first time. Another 30-40% were part of a second therapy group of patients who were making their first switch to a different HIV treatment regimen. Only approximately 20% of patients (i.e., those who were not part of the initial or second therapy groups) were in a rescue situation, looking for a drug that would control their viral load after the virus developed a resistance to other combinations of HIV drug therapies.

199. In other words, as a result of the manner in which Viread was approved by the FDA, roughly 60% of the available HIV patient pool was unavailable to Defendants. However, Viread was aggressively and illegally marketed in order to open up the maximum potential patient pool. As a result, Viread was prescribed off-label to these patients. Therefore, according to several Confidential Witnesses, including CW1, Defendants instructed Viread sales representatives to promote studies (i.e., Study 903) on the effect of Viread on initial or first-line therapy patients to foster increased sales. Defendants further publicized new studies on Viread and provided them to their sales and marketing staff in an attempt to change physicians’ views on the drug and achieve sales beyond the patients authorized by the FDA.

200. Defendants’ off-label campaign succeeded. CW1 sold approximately $3 million of Viread during his tenure at Gilead. According to CW1, approximately 85% to 95% of all of CW1’s Viread sales arose from off-label promotion. In fact, CW1 did not have a single sales contact where
of off-label information was not used to market Viread. According to CW1, the Company provided so much off-label data and was so forceful in instructing sales representatives to utilize off-label information that off-label information was the cornerstone of Gilead’s Viread marketing efforts. This unequivocal sentiment was echoed by several other Confidential Witnesses. According to many Confidential Witnesses, off-label marketing took three forms: (1) marketing to HIV patients co-infected with Hepatitis B; (2) marketing Viread as a first-line or initial therapy for HIV infection; and (3) marketing against Viread’s safety profile.

201. CW2’s experiences mirror CW1’s and CW2 corroborates CW1’s analysis of the material impact of off-label marketing on Gilead’s sales of Viread. To be sure, CW2’s Viread sales were also based, in very large measure, on off-label marketing. CW2’s sales analysis can be divided into two parts: before and after Georgia, CW2’s territory, added Viread to its formulary list for the federal AIDS Drug Assistance Program (“ADAP”) system.

202. According to the U.S. Department of Health and Human Services, ADAP provides medications for the treatment of HIV disease. The program is funded through Title II of the Ryan White CARE Act, which provides grants to States and Territories. Through ADAP, grants are awarded to all 50 States. Specifically, Congress earmarks funds that must be used for ADAP. The ADAP “earmark” has increased more than 1,000 percent over the past five years, from $52 million in 1996 to $639 million in 2002. But, total ADAP spending is even higher, since State ADAPs also receive money from their respective States, other CARE Act programs, and through cost-savings strategies.

203. Approximately 128,078 people received medications through ADAP in 2000. None had adequate health insurance or the financial resources necessary to cover the cost of medications. On average, 73,000 clients are served each month. The ADAP in each State and Territory is unique in that it decides which medications will be included in its formulary, and how those medications will be distributed. Each State and Territory establishes its own eligibility criteria. All require that individuals document their HIV status. Fifteen States have established income eligibility at 200% or less of the Federal Poverty Level (“FPL”). Nationally, more than 80% of ADAP clients have incomes at 200 percent or less of the FPL. See http://hab.hrsa.gov/programs/factsheets/adap1.htm.
204. According to CW2, inclusion in the ADAP formulary means that all AIDS/HIV patients covered by the program receive the drug and sales increase exponentially. Prior to Viread’s inclusion in the Georgia ADAP formulary, CW2 sold approximately between $10 million and $15 million of Viread. Of those sales, CW2 estimates that 85%-90% were a result of off-label marketing. After inclusion of the Georgia ADAP formulary (late 2002 through early 2004), CW2 sold approximately between $15 million and $20 million of Viread. Again, CW2 states that 85%-90% of those sales were caused by off-label marketing. Like other Confidential Witnesses, CW2’s off-label marketing involved: (1) marketing to HIV patients co-infected with Hepatitis B; (2) marketing Viread as a first-line or initial therapy; and (3) marketing against Viread’s safety profile.

205. Based on his/her own off-label Viread sales, CW1 believes that 75%-95% of all sales of Viread in the United States were the result of off-label marketing. Indeed, one has only to compare Gilead’s explosive growth from 2002 to 2003 to see the effect that off-label marketing had. Viread sales in the first quarter of 2002 were $27.1 million, compared with $107 million in the first quarter of 2003. Viread sales in the second quarter of 2003 were a whopping $167 million – up from $44.7 million in the second quarter of 2002. Indeed, CW3 recalled that treatment naïve sales grew dramatically as the Company made a push to increase sales through off-label marketing at the end of 2002 and beginning of 2003.

206. CW6’s experience selling Viread off-label in the New York City market led her/him to estimate that at least 70% of her/his sales were off-label for use by treatment naïve patients. Adding in the fact that she/he was also encouraged to market Viread off-label to Hepatitis patients, and CW6’s experiences corroborate CW1 and CW2’s estimates of the extent of Gilead’s off-label sales. Specifically, CW6 stated her/his total sales of Viread for the 2003 timeframe were approximately $400,000 to $500,000 per month. Thus, during 2003, CW6 sold approximately between $4,800,000 and $6,000,000 of Viread, of which at least between $3,360,000 and $4,200,000 (i.e., 70%) resulted from off-label marketing and sales. Taking out the dramatic impact of off-label marketing to treatment naïve patients, CW6 would have only sold between $120,000 and $150,000 of Viread per month during 2003, for a total of between $1,440,000 and $1,800,000 for all of 2003.
Moreover, Gilead's domestic Viread sales were $115.6 million in the second quarter of 2003, compared with $29.2 million in the second quarter of 2002. Based on CW1’s information, which is bolstered by the accounts of all the Confidential Witnesses, off-label sales accounted for between $86.7 million and $109.82 million in the second quarter of 2003. The staggering impact of off-label marketing is underscored by the seriousness of the off-label marketing as described in the Untitled Letter and the FDA Warning Letter.

As set forth by many Confidential Witnesses, the use of off-label marketing of Viread was pervasive. According to CW1, sales representatives would discuss amongst themselves which off-label materials and marketing tactics were generating the most sales. CW1 knows this because of CW1’s experiences on the Gilead Field Marketing Advisory Committee, which exposed CW1 to Therapeutic Specialists and Gilead executives from all regions of the United States. In addition, CW1 would discuss sales techniques with successful Therapeutic Specialists in other regions of the country in an effort to find out what methods worked best for them. These discussions included descriptions of off-label marketing techniques. In addition, according to a former Therapeutic Specialist who was part of Viread’s launch and with the Company through June 2002, the sales force was supplied with documents listing physicians and a profile of the drugs they prescribed. The list would allow sales representatives to tailor their Viread pitch to suit the prescribing patterns of the various doctors and explain why Viread was superior to the drugs the physician had been prescribing.

As a result of Defendants’ off-market labeling, physicians prescribed Viread for purposes not specifically approved by the FDA. For example, according to an AIDS-specialist physician who treats between 2,000 and 2,500 AIDS patients in the Western United States, he routinely uses Viread off-label to treat Hepatitis B co-infected HIV patients. In addition, this physician began using Viread as a first line antiretroviral therapy in early 2003, before it was approved by the FDA in late 2003 for this purpose, in response to unsolicited data this physician received from Gilead concerning Study 903 and the use of Viread in treatment naïve patients.

As described above, during the Class Period Viread was never indicated for treatment in patients who are co-infected with HIV and Hepatitis B – the FDA had not approved such a use of
Viread and thus prohibited any marketing of Viread for treatment of co-infected patients. In fact, the
FDA warned against this practice, as described above, in a black box warning – the strongest
warning possible – in the Viread label.4

211. Additional data supports the accounts of the Confidential Witnesses. According to
the “HIV Therapy Audit,” a quarterly physician survey designed to monitor HIV+/AIDS patients
who are seeking treatment and their associated drug and non-drug therapy that was conducted by
Verispan, LLC,5 HIV patients co-infected with Hepatitis B first began using Viread in the third
quarter of 2002. At that time, 55.5% of co-infected patients surveyed used Viread. By the third
quarter of 2003, 72.7% of co-infected patients surveyed were using Viread, despite the fact that: (1)
no data existed that conclusively demonstrates that Viread effectively treats Hepatitis B infection,
with or without HIV co-infection; (2) the FDA had never approved of the use of Viread in HIV and
Hepatitis B co-infected patients and, indeed, specifically warned against it; and (3) HIV resistance to
antiretrovirals, such as Viread, leads HIV positive patients to change their drug regimens, exposing
co-infected patients using Viread to severe acute exacerbations of Hepatitis B infection.

212. The 72.7% from the third quarter of 2003 figure translates into roughly 26,000
patients, based on the fact that roughly 10% of the HIV infected population are co-infected with
Hepatitis B, and approximately 360,000 HIV patients receive antiretroviral treatment such as Viread.

4 The FDA warning label for Viread also advised healthcare professionals to check HIV patients for
Hepatitis B co-infection, prior to the patients taking any Viread, to prevent instances of liver failure
in the event an HIV patient has to change his or her drug regimen and stop taking Viread due to HIV
resistance.

5 Verispan describes itself as “revolutionary health care information company” that “is the leading
provider of patient-centric, longitudinal data delivered in near real time as well as one of the major
providers of health care information overall.” “Verispan has secured rights to data from more than
half of all U.S. prescriptions and over 20% of all U.S. electronic medical transactions annually.
Verispan captures at least 25% of all prescriptions from 98% of all three-digit zip codes and at least
45% of all prescriptions from almost 80% of all zip codes. This pervasive data coverage means that
Verispan can provide better insight into prescription and medical activity at the national, regional
and individual prescriber level than ever before possible.” See http://www.verispan.com/about/.
This data is bolstered by the account of CW7, who stated that 10% of her/his total Viread sales were to Hepatitis B infected patients.

213. Defendants also increased Viread sales by improperly marketing Viread as a first-line (initial) therapy for treatment naïve HIV patients, before Viread was indicated for these patients. Until late 2003, Viread was not indicated for use in treatment naïve patients. Not content to await FDA approval of Viread as a first-line antiretroviral drug, Defendants immediately used off-label marketing to sell Viread as a first-line HIV therapy upon launching Viread in October 2001.

214. According to an Infectious Disease Specialist in the Southeast United States with a large AIDS practice that comprises 40% to 45% of his total practice, he began to receive unsolicited advice on using Viread as a first line HIV therapy from Gilead sales representatives shortly after Viread was launched in October 2001. He then began to use Viread as a first line therapy in 2002. A second Infectious Disease Specialist in the Southeast United States also received unsolicited material from Gilead representatives on the use of Viread as first line therapy upon Viread’s October 2001 launch. The second Infectious Disease Specialist began using Viread as a first line therapy in 2001.

215. According to the HIV Therapy Audit, in the fourth quarter of 2001 (shortly after its launch), approximately 11.2% of patients taking Viread in the U.S. were using it as a first-line treatment. By the third quarter of 2003, Defendants’ improper off-label marketing had increased that number had to 23.8%. Thus, out of roughly 83,000 patients on Viread by the third quarter of 2003 (according to the HIV Therapy Audit), almost 20,000 were using Viread as a first-line therapy.

216. Gilead also marketed Viread against its safety label. Gilead sales representatives routinely represented that Viread had no side effects and was as safe as placebo. Martin called it a "miracle product." According to the Medical Director of a large AIDS clinic in Washington, D.C. who uses Viread routinely in patients, Gilead representatives told him that Viread was completely safe – as safe as placebo. In particular, the Medical Director said that the Gilead representatives

Likewise, an informal survey of AIDS physicians resulted in reported co-infection rates of between 5% and 30%.
marketed Viread as completely safe with regard to renal function. The Medical Director stated that based on these false representations (off-label marketing), he wrote prescriptions for Viread. Since prescribing Viread based on false safety marketing, the Medical Director has had patients develop renal (kidney) failure due to Viread and is now cautious about using Viread. This Medical Director stated that he felt he had been deceived about Viread’s safety profile by Gilead drug sales representatives.

217. Similarly, an AIDS specialist from the Western United States was told by Gilead representatives that Viread was a safe drug without nephrotoxicity (risk of renal problems). This AIDS specialist has since found that nephrotoxicity is a problem with Viread – contrary to what Gilead sales representatives told her. Likewise, a Doctor of Pharmacy practicing in the Mid-West United States, who has 20% of the patients in her AIDS clinic on Viread, was told by Gilead sales representatives that Viread had a safety profile similar to placebo. Since then, she has seen increasing frequency of renal insufficiency in patients on Viread – in direct contravention to Gilead’s off-label marketing tactics.

218. The Verispan data, the data collected from public sources, and the estimates of confidential sources, including many physicians, demonstrate that extraordinary amounts of Viread were prescribed as a direct result of Defendants’ off-label marketing. Extrapolating from Verispan’s survey data, nearly 20,000 patients were taking Viread as a first-line therapy, 26,000 co-infected patients were taking Viread, and certainly large numbers of Viread patients were obtained by marketing against the safety label. This data, which includes the Verispan data, is therefore in line with and corroborates all of the Confidential Witnesses’ estimates that off-label marketing formed the basis for the Company’s sales culture, including CW1 and CW2’s estimates that 75% to 95% of Viread sales during the Class Period were caused by off-label marketing, and CW6’s estimate that at least 70% of her/his Viread sales were caused by off-label marketing to treatment naïve patients.

219. The Verispan data is based on surveys of physicians. As a result, it is not a complete picture of Viread’s use as a result of off-label marketing. Gilead’s financial statements in their SEC filings, however, corroborate the Verispan data. Gilead’s financial data shows Viread sales growing from its launch through the Class Period from revenue of $13 million to revenue of $115 million. At
the same time, Viread sales became a larger percentage of Gilead’s total sales from 22.1% at the fourth quarter of 2001 to 59.5% at the third quarter of 2003.

220. Whether using the data extrapolated from Verispan, whether using the 75% to 95% estimate of Viread sales resulting from off-label marketing as calculated by CW1 and CW2, the 70%-plus estimate calculated by CW2, or whether taking into account the collective experiences of all of the Confidential Witnesses, the results are not only material, but stunning.

221. Defendants will likely (because they have in the past) argue that the fact that 75% - 95% of CW1’s and CW2’s sales of Viread, as well as at least 70% of CW6’s sales of Viread, were a direct result of off-label marketing (amounts that Gilead cannot dispute are material) does not mean that 75% - 95% of Gilead’s Viread sales were caused by off-label marketing. However, taking all of the allegations of this Complaint as true, it is clear that the Court should draw an inference that Gilead’s company-wide Viread sales were materially artificially inflated as a direct result of off-label marketing.

222. The inference that Gilead’s Viread sales were materially artificially inflated by off-label marketing is supported by, among other things: (1) the intensity and frequency with which Gilead ordered its sales force to use off-label marketing; (2) the pressure put on all of the Confidential Witnesses to disseminate and actually utilize off-label marketing; (3) the volume of CW1, CW2, and CW6’s Viread sales caused by off-label marketing; (4) the fact that off-label marketing materials were deliberately delivered to the sales force through the Company’s training department; (5) the FDA letters, which corroborate the Confidential Witness allegations that there was a deliberate, covert effort to engage in systemic off-label marketing; (6) the statistical evidence of the levels of off-label sales; and (7) the familiarity that CW1 (especially as part of the Field Advisory Board) and CW2 have with other Gilead sales people and their knowledge that other Gilead sales people use off-label marketing to sell Viread.

223. Indeed, every indication is that the use and impact of the off-label marketing was across-the-board. Even if the Court were to, for the sake of argument, cut CW1’s and CW2’s estimates in half, to 35% - 45%, the impact of off-label marketing is material.
E. The Effect of Defendants’ Fraudulent Promotion of Viread on Drug Wholesalers and Wholesaler Inventory Over-Stocking

224. At all relevant times, the major national wholesalers of Viread were McKesson Corp., Cardinal Health, Inc., and AmeriSource-Bergen Corp.

225. According to a former Vice President/Division Manager of national wholesaler AmeriSource-Bergen, the major national wholesalers purchase approximately ninety-percent (90%) of the drugs sold by drug manufacturers.

226. It is common knowledge among industry insiders, including Defendants, that wholesalers make very little, if any, profit when re-selling manufacturers’ drugs purchased at their usual price. In fact, according to a former Marketing Manager for national wholesaler Bergen Brunswig, wholesalers generally only realize a profit when they sell products to retailers at minimal margins, or when they stockpile mass quantities of the product prior to a price increase and then sell it at the new price. Wholesalers do this by overstocking a product at the lower price.

227. Several former Gilead employees including CW1 and CW2, a Director of National Sales, and a Regional Sales Director, confirmed that like others in the industry, Gilead executives and employees were well aware of this business strategy. In fact, according to a former Gilead Regional Sales Director, while at the San Francisco National Meeting, Defendant Perry acknowledged to several employees that wholesalers were overstocking in anticipation of a Gilead price increase. Indeed, this “buy at the old price, sell at the new price” business plan is so widely relied upon that the national wholesalers have employees whose only job is to meet with manufacturers, find out when price increases are going to take place, and assist their purchasing departments with overstocking the drugs.

228. Likewise, drug manufacturers employ trade relations people whose job is to interact with drug wholesalers and provide them with information about upcoming price increases and other product information. According to CW1, Gilead employed at least two people in this capacity.

229. As described by these industry insiders, drug manufacturers such as Gilead not only know about the “buy at the old price, sell at the new price” wholesaler strategy, but encourage and perpetuate it. They do this by informing wholesalers in advance that a price increase is going to take place.
place. Gilead did just that, artificially boosting sales of Viread, in conjunction with its false, misleading and illegal promotion of Viread, and announced to wholesalers that a price increase for Viread would take effect in June 2003. Consequently, motivated by the temptation of increased margins and emboldened by Gilead's illegally inflated sales and artificially inflated demand for Viread, the major drug wholesalers stockpiled mass quantities of Viread in advance of the June 2003 price increase. This wholesaler stockpiling would not have occurred but for the off-label marketing and the resulting creation of an artificially increased demand for Viread. Thus, the wholesaler overstocking was also caused by Gilead's illegal off-label marketing scheme.

230. By increasing the price of Viread in June 2003, Defendants furthered their fraudulent scheme. Conveniently, the resulting wholesaler overstock confirmed the impression that Viread was in high demand and that Gilead's financial and operational results were strong.

231. Defendants routinely used wholesaler sales to improve overall Viread sales. For example, on April 2, 2003, Meyers sent an e-mail to sales representatives, including Rich, DelloStritto, and Kaiser, among others, discussing the need to meet sales figures for Viread. The e-mail was copied to, among others, defendants Martin, Perry, Milligan, and Bischofberger. Attached to the e-mail was a chart entitled "Kicker Bonus Forecast." The Kicker Bonus Forecast set forth Viread's Financial Forecast of sales from October 2002 through April 2003 and the corresponding actual sales. The chart indicated that to meet the seven month sales forecast, April's actual Viread sales needed to be $38.3 million, $7 million more than the April forecast of $31.9 million. According to CW1, Gilead made the sales numbers by overloading wholesalers with product. Wholesalers were willing to overstock because they were tricked into believing that the off-label marketing-created "demand" for Viread was real.

DEFENDANTS' CLASS PERIOD MATERIALLY FALSE AND MISLEADING STATEMENTS

232. The Class Period begins on July 14, 2003. On that date, Gilead issued a press release entitled "Gilead Sciences Expects Second Quarter 2003 Financial Results Will Exceed Expectations" and reported that, because of dramatically increased demand for Viread, its financial results for the
previous quarter (Second Quarter 2003) would “exceed expectations.” In pertinent part the Company stated:

Gilead Sciences, Inc. today announced that based on initial analyses, the company expects that its financial results for the second quarter 2003 will exceed analyst expectations, driven primarily by higher product revenues.

Gilead estimates its total net revenues for the second quarter 2003 will be in the range of $236-239 million. Median total net revenues projected by analysts who report their earnings forecasts to FirstCall are $179 million. The increase in revenue was driven primarily by strong sales growth of Viread® (tenofovir disoproxil fumarate), one of the company's antiviral drugs for the treatment of HIV. Gilead expects that Viread sales will be approximately $165 million for the quarter, compared to $107 million for the first quarter of 2003. Increasing Viread sales reflect broader prescribing patterns in all commercial markets, as well as increases in U.S. wholesaler inventory levels in the second quarter in anticipation of a Viread price increase, which was implemented on June 27, 2003.

(Emphasis added.)

233. Defendants' statements in this press release regarding Gilead's sales of Viread, including sales results and the reasons for increased Viread sales, were materially false and misleading because, as detailed in the Section entitled "Factual Detail Undermining the Truth of Defendants' Class Period Representations," Defendants' marketing and promotional activities for Viread were not in compliance with FDA approved guidelines, violated federal laws, and created serious public health and safety implications for Viread users. Defendants' false, misleading, and illegal marketing and promotional activities prior to and during the Class Period had the cause and effect of materially increasing the volume of prescriptions for Viread at all relevant times. Their activities also had the cause and effect of materially boosting the Viread inventory of U.S. drug wholesalers. Defendants' fraudulent Viread promotional scheme was designed to, and did, create the false and misleading public impression that demand for Viread was strong and that Viread sales would continue to increase.

234. Analysts and the market took Defendants' July 14, 2003 press release as welcome news. Analyst Eric Schmidt of SG Cowen Securities expressed amazement at Gilead's ability to beat expectations by such a wide margin. A July 14, 2003 Bloomberg News report quoted Schmidt as follows:
"The earnings could be as high as double the Street consensus, which would really be remarkable," said Schmidt, who rates Gilead shares "market perform" and doesn’t own them. "I can’t remember a biotech company of this size beating expectations by two-fold before."

235. Analysts cautioned that Viread sales may have been driven materially by wholesalers stocking up ahead of a June 2003 price increase, signaling weak demand for Viread. In this regard Bloomberg News reported:

It’s not clear how much of the increase in Viread sales came as wholesalers stocked up on the drug ahead of a price increase that took effect last month, said Michael King, an analyst at Banc of America Securities. “I’m going to be a little bit careful about whether the second-quarter Viread numbers represent a new level because of the inventory,” said King, who rates the stock “buy” and owns none.

236. As a result, Defendants acted quickly to neutralize analyst concerns, assuring investors that increased prescriptions (indicating increased demand) were driving Viread sales, in addition to any inventory overstocking.

237. Specifically, on July 14, 2003, Gilead’s spokeswoman, Amy Flood, stated in Bloomberg News: “[t]he main reason for the jump in Viread sales is an increase in prescriptions, not inventory stocking.”

238. In response to the July 14, 2003 news, the price of Gilead shares soared by $7.97 per share in one day, closing at $67.25 on July 14, 2003 (up from the previous day’s close of $59.28 per share) – a single day increase of 13.4% and a near-record high.

239. Notwithstanding, Amy Flood’s July 14, 2003 statement was false and misleading because it was designed to, and did, create the false impression that demand for Viread was strong. In reality, as detailed herein, Defendants’ false, misleading and illegal marketing and promotion of Viread was artificially boosting sales of and demand for Viread, which in turn persuaded wholesalers to overstock Viread in response to the announced price increases.

240. Just days after Gilead’s announcement of its second quarter 2003 results, on July 29, 2003, the DDMAC issued the FDA Warning Letter. The letter was addressed to Defendant Martin and required Gilead to cease and desist from its repetitive, illegal promotion of Viread. The FDA was particularly concerned about Gilead’s illegal practices because of significant public health and safety concerns, Gilead’s blatant disregard of the FDA’s prior written warnings, and because of
illegal promotional practices at the well-attended Miami conference on March 31-April 2, 2003. See ¶178-86, supra. After that conference, attended by more than 1,500 guests seeking information regarding the efficacy of Viread, Gilead reported outstanding sales increases for Viread during Second Quarter 2003 (which included April, May and June 2003, the months following the Miami conference).

Indeed, on July 31, 2003, the Company issued a press release reporting its Second Quarter 2003 results and announcing that revenues for the quarter were reportedly $238.9 million, in line with its July 14, 2003 preannouncement:

Net revenues from product sales totaled $230.7 million, up 146 percent from the second quarter of 2002. This growth primarily was driven by higher revenues from Viread® (tenofovir disoproxil fumarate). Sales of Viread were $167.0 million in the second quarter of 2003, up from $44.7 million in the second quarter of 2002 and $107.3 million in the first quarter of 2003. Viread sales growth was primarily driven by higher prescription volume, a significant increase in U.S. wholesaler inventories and a favorable European currency environment compared to the same quarter last year. Gilead estimates that increased stocking by U.S. wholesalers accounted for $25-30 million of Viread sales in the second quarter. AmBisome® (amphotericin B) liposome for injection sales for the second quarter of 2003 were $51.2 million, an increase of 7 percent compared to the second quarter of 2002. Reported AmBisome sales in the second quarter of 2003 were $7.0 million higher due to the favorable currency environment compared to the same quarter last year. On a volume basis, AmBisome sales decreased by 4 percent in Europe compared to the second quarter 2002. Sales of Hepsera® (adefovir dipivoxil 10 mg) totaled $12.4 million for the second quarter of 2003, up from $5.8 million in the first quarter of 2003.

“We are very pleased to report another quarter of significant increases in product revenues. This strong growth was fueled primarily by increasing sales of Viread in all marketed territories and Hepsera’s uptake in the United States and introduction in Europe,” said John C. Martin, PhD, President and Chief Executive Officer of Gilead Sciences. “We are focused on continuing this sales momentum and increasing our market share through robust clinical data and label expansions in key territories, as well as launching Emtriva™ (emtricitabine) for HIV.”

(Emphasis added.)
release the FDA had issued repeated warnings and cease and desist instructions to Gilead (addressed
to Defendant Martin) for its illegal Viread promotional campaign.

243. Market analysts took note of the announced wholesaler overstocking and took it into
account in their assessment of Viread’s performance. Even with the overstocking, however, analysts
were impressed with Gilead’s second quarter results.

244. For instance, on July 31, 2003 Morgan Stanley issued a research note titled, “Gilead
Sciences: Still Something Left on the Table.” The note attributed Gilead’s second quarter results to
“broader prescribing patterns and market share gains in all markets, currency benefit in Europe ... as well as the increase in US wholesaler inventories.” The increased inventories did not concern Morgan Stanley, however, because it believed that, in light of Viread’s strong growth, wholesaler inventories had been historically low. In Morgan Stanley’s estimation, Viread’s performance justified higher inventory levels, and thus, it did not expect that the overstocking would damage Viread’s third quarter performance too badly: “We estimate that US wholesaler inventories were about 3.5 weeks entering 2Q, versus an average of about 4.5 weeks for Viread historically and a pharmaceutical industry average of about 5.8 weeks. Thus, we believe that there will be a limited impact of inventory draw-down in 3Q . . . .”

245. On August 1, 2003, Prudential Financial issued a report attributing the stellar second
quarter results to “stronger than expected prescription data, an increase in U.S. inventory levels, and favorable foreign exchange rates.” Prudential estimated that industry stocking, plus the foreign exchange benefit, to total $35 million. Even taking the overstock into account, the strong demand for Viread persuaded Prudential that full year sales of the drug would total $625 million.

246. Even as late as October 8, 2003, Bear Stearns projected third quarter Viread sales of
$136 million — a figure that, it said, took into account an estimated $30 million of wholesaler
inventory build-up in the second quarter of 2003.

247. Unbeknownst to the market, however, the favorable results that Gilead had reported
had been based on artificially inflated demand as a result of illegal off-label marketing. Artificially inflated demand not only fueled prescriptions and sales, but had also induced wholesalers to stock up
on Viread. These wholesalers had purchased the extra Viread in anticipation of continued strong
growth in demand for the drug.

248. As analysts were touting Viread's strong second quarter performance, just three
business days after the FDA Warning Letter issued -- but before it was disclosed to the market -- on
August 5, 2003 Defendants began dumping their Gilead common stock at a furious pace. In total,
the Individual Defendants sold 324,601 shares of Gilead at artificially inflated prices in a single
month, reaping gross proceeds of $20,682,070.78. The average selling price was $64.10 per share,
near the stock's peak at $70.61 per share.

249. On August 7, 2003, the FDA Warning Letter became public. Investors, aware of the
letter but unaware of the extent to which Gilead's entire business model depended on off-label
marketing, did not attribute much significance to it.

250. For instance, postings on the Yahoo! Message Board devoted to Gilead on August 7,
2003 show that although investors were concerned about the FDA Warning Letter, they
(erroneously) believed that the problems were likely confined to a few rogue salespersons. One user
posted, "Its not that hard to sell a great drug guys!!! [sic] - Would someone at GILD please find the
dumbass sales reps that keep talking out their ass and have them or the VP in charge of sales and
marketing fired before more embarrasement occurs. [sic]" In another message, the poster said:
"[A]fter reviewing the specifics, it is clear this is nothing new and a standard reprimand -- I doubt
this will move the stock one penny ...."

251. Another poster wrote, "Relax .... This is a standard tactic that the FDA starts to
utilize when a drug becomes the market leader. This is done primarily to keep the company in
line .... Big pharma gets these letters on a monthly basis ...." Another poster agreed, writing "I
couldn't agree more. FDA always do things like that to cover their ass just, and I mean just, in case
if something happens. [sic]"

252. Investors apparently believed that the FDA Warning Letter referred to stale
transgressions with little implication for ongoing sales. One Yahoo! poster wrote, "Yeah, real timely
information. In a letter dated July 29th, about marketing claims in April Whatever, its old news.
Another wrote, “This report is as dated and irrelevant to the future growth prospectus of GILD as the EU advisory was relating to Glaxo’s study and dated results.”

In short, although investors took notice of the FDA Warning Letter, they did not recognize its significance because they did not understand the scope of the off-label marketing and thus could not understand how the FDA’s warning would impact sales.


The Second Quarter 2003 10-Q confirmed the previously announced financial results, stating:

**Net product sales** were $230.7 million for the three months ended June 30, 2003, compared with $93.8 million for the quarter ended June 30, 2002, representing an increase of 146%. **The increase in product sales is due to the significant increase in the volume of sales of Viread.** Sales of Viread in the second quarter of 2003 were $167.0 million, or 72% of total product sales, compared to $44.7 million, or 48% of total product sales, in the second quarter of 2002. Of the $167.0 million, $115.6 million were U.S. sales and $51.4 million were international sales. International sales of Viread in the second quarter of 2003 were positively impacted by $5.0 million due to a more favorable currency environment compared to the second quarter of 2002. **We believe U.S. sales in the second quarter were favorably impacted by an increase in wholesaler stocking levels in anticipation of a price increase. We estimate that this higher stocking resulted in $25.0 to $30.0 million of additional sales during the second quarter,** which may adversely impact sales in the third quarter as wholesalers return to more normal inventory levels and buying patterns. We expect Viread sales to be in the range of $550 million to $600 million for the full year 2003.

* * *

In the first six months of 2003, net product sales were $386.6 million, versus $164.5 million in the comparable period of 2002, an increase of 135%. Sales of Viread for the six months ended June 30, 2003 were $274.3 million, or 71% of total product sales, compared to $71.9 million, or 44% of total product sales, in the six months ended June 30, 2002. **The significant increase in Viread sales is due to increased prescription volume and an increase in U.S. wholesaler inventory levels.** Of the $274.3 million in Viread sales, $184.5 million were U.S. sales and $89.8 million were international sales. International sales of Viread in the first six months of 2003 were positively impacted by $8.6 million due to the more favorable currency environment compared to the same period last year. We also recognized $92.2 million in AmBisome sales for the first six months of 2003, a 5% increase over the six months ended June 30, 2002. Reported AmBisome sales in the first six months of 2003 were $13.2 million higher due to the favorable currency environment. On a volume basis, however, AmBisome sales decreased by 7% in Europe due to increased competition.

(Emphasis added.)
256. The statements in the Second Quarter 2003 10-Q were false and misleading for the same reasons detailed in ¶¶233 and 242 herein. Defendants' fraudulent promotion of Viread was at the core of increased Viread prescriptions. Increased Viread prescriptions contributed to Gilead's ability to increase the price of Viread in June 2003 which, in turn, increased U.S. drug wholesalers' motivation to overstock their Viread inventory. Defendants' lack of candor regarding the true reasons for Viread's success allowed Defendants to unload millions of dollars worth of Gilead stock.

257. While Defendants' Second Quarter 2003 10-Q briefly addressed the FDA Warning Letter, it did nothing more than disclose its existence; it failed to provide anything close to full and complete disclosure of Defendants' pervasive fraudulent marketing scheme, stating:

Regulatory Process. The products that we develop must be approved for marketing and sale and will be subject to extensive regulation by the FDA and comparable regulatory agencies in other countries. In addition, even after our products are marketed, the products and their manufacturers are subject to continual review. We are continuing clinical trials for AmBisome, Viread, Hepsera and Emtriva for currently approved and additional uses and anticipate filing for marketing approval of additional products over the next several years. If products fail to receive marketing approval on a timely basis, or if approved products are the subject of regulatory changes, actions or recalls, our results of operations may be adversely affected. For example, on August 7th, 2003, the FDA issued a written warning concerning our promotional practices of Viread. The FDA could seek to impose penalties including fines, suspensions of regulatory approvals or promotional activities for a product, product recalls, seizure of products and criminal prosecution if our promotional practices violate federal regulations in the future or we otherwise fail to comply with FDA regulations.

Contrary to Defendants' Second Quarter 2003 Form 10-Q, the FDA Warning Letter was issued on July 29, 2003, not August 7, 2003. See Exhibit F. Rather, the FDA made the Warning Letter public on August 7, 2003. This distinction is important because, as demonstrated by the Individual Defendants' trading records below, Defendants Perry and Bischofberger began unloading their shares of Gilead stock after the Warning Letter was issued, but prior to its public disclosure. Specifically, Defendants Perry and Bischofberger sold more than $3,000,000 worth of stock each between the date the FDA issued the Warning Letter and the date the FDA made the Warning Letter public. Similarly, Defendant Milligan sold almost $700,000 worth of stock on August 7, 2003, the very same day the Warning Letter became public. The very next day, on August 8, 2003, Defendant Martin sold more than $3,000,000 worth of stock.
258. Unbeknownst to investors, the disclosure of the FDA Warning Letter had a detrimental effect on Viread sales. Physicians, now alerted to Gilead’s illegal marketing efforts and to the safety problems with Viread, were less eager to prescribe it to their patients. Competitors were able to use the FDA Warning Letter as an argument to physicians to choose their own products over Viread.

259. Gilead saw a marked drop in prescriptions and sales in the weeks following the disclosure of the letter. Even after prescriptions and sales recovered late in the Third Quarter, they did not go as high as they would have had the letter not issued. Although precise sales figures in the aftermath of the disclosure of the FDA Warning Letter are exclusively in the hands of Defendants, wholesalers, and certain third party organizations that track prescription drug sales (and are not available to Plaintiffs for use at this stage of the litigation), Morgan Stanley’s October 29, 2003 report includes a chart of Viread prescriptions on a weekly basis demonstrating a sharp drop in August 2003, and flattened growth for the rest of the third quarter, as compared to previous quarters.

260. Viread prescriptions would have fallen even further in the weeks following the disclosure of the FDA Warning Letter, but for the fact that side-effects rendered it dangerous for certain patients to discontinue the drug, as described supra at ¶131. Overall, the disclosure of the FDA Warning Letter in the Third Quarter resulted in sales and prescription for the quarter that did not demonstrate the strong growth that investors had come to expect.

261. The slow down in growth, coupled with the drop in sales and prescriptions immediately following the FDA Warning Letter disclosure, influenced wholesalers, who monitored sales of Viread very closely in order to gauge how much inventory to keep on hand. Without the strong continued demand that they had come to expect from Viread, wholesalers chose to draw down much more of the excess inventory than they otherwise would have done. As a result, by the end of the quarter, wholesalers reduced their inventories of Viread to as little as two weeks’ supply, far beneath historical levels for Viread, beneath the industry average of 5.8 weeks, and well beneath what would have been expected had Viread’s performance been an accurate reflection of legal demand. In fact, inventory levels were at the lowest level they had been in four quarters.
262. On October 28, 2003, after the markets closed, Defendants issued a press release reporting Gilead’s Third Quarter 2003 financial results and revealing that Viread sales for that quarter would be materially less than expected due to the fact that the level of overstocking by wholesalers was substantially and materially more than previously reported. The press release explained that, as a result, demand for Viread in the third quarter of 2003 was met by sales from existing wholesaler inventory, rather than new sales, stating:

Net revenues from product sales totaled $194.1 million, up 61 percent from the third quarter of 2002. This growth primarily was driven by higher revenues from Viread® (tenofovir disoproxil fumarate). Sales of Viread were $115.4 million in the third quarter of 2003, up from $68.9 million in the third quarter of 2002, an increase of 67 percent. U.S. sales of Viread were $59.4 million, and sales outside the United States totaled $56.0 million. Viread sales growth was primarily driven by higher prescription volumes in both the United States and Europe and a favorable European currency environment compared to the same quarter last year. After reviewing NDC prescription trend, IMS inventory data and actual Viread sales, Gilead estimates there was approximately $33 to $37 million of inventory reduction by U.S. pharmaceutical wholesalers during the third quarter of 2003 following an equivalent inventory build during the second quarter of 2003. AmBisome® (amphotericin B) liposome for injection sales for the third quarter of 2003 were $51.6 million, a record high and an increase of 6 percent compared to the third quarter of 2002. Reported AmBisome sales in the third quarter of 2003 were $6.1 million higher due to the favorable currency environment compared to the same quarter last year. On a volume basis, AmBisome sales decreased by one percent in Europe compared to the third quarter of 2002. Sales of Hepsera® (adefovir dipivoxil 10 mg) totaled $16.4 million for the third quarter of 2003, up from $12.4 million in the second quarter of 2003. Since the launch of Emtriva™ (emtricitabine) in July 2003, sales for the third quarter of 2003 were $6.0 million.

(Emphasis added.)

263. The market was stunned by this news. Not only was demand for Viread well below what had been expected, but, contrary to expectations, wholesalers had drawn down the entire amount of the second quarter overstocking rather than purchase additional supplies of Viread. For instance, on October 29, 2003, Bear Stearns issued a research note reporting that Viread wholesale stocking levels were as low as they could possibly get at the two week level. Bear Stearns promptly lowered its fourth quarter projections "[b]ased on estimation of lower end-user demand."

264. Morgan Stanley also attributed the disappointing results to “lower end-user demand” and the striking degree to which wholesalers had dumped their Viread supplies rather than refill their inventories: “Wholesalers appear to have managed down their inventory levels for Viread, at least in the short term, from the one-month level previously, to about half of that now. The result of higher
inventories entering the quarter, lower end-user demand entering the quarter, and lower wholesaler
target inventories, had a significant effect on the reported 3Q Viread number.”

265. The disappointing news — lower demand, resulting in wholesalers’ decision to reduce
their supplies to levels well below what they had been before the overstocking — caused the market
to punish Gilead’s stock price. Shares of Gilead fell 12%, or $7.46 per share, from a high of $59.46
per share on October 28, 2003, to a low of $50.27 and closing at $52.00 per share on October 29,
2003. The news also sparked enormous trading volume of 66 million Gilead shares, compared to the
average daily volume of 4.6 million – a 1400% increase. The October 28, 2003 press release tacitly
admitted that demand for Viread was not as strong as investors were previously led to believe. U.S.
drug wholesalers were drawing down very material amounts of Viread inventory and Defendants’
fraudulent promotion of Viread, which artificially boosted Viread sales, was continuing to have very
detrimental effects on the Company’s ability to sustain its sales, financial and operational results.

266. A reasonable investor would consider Defendants’ misrepresentations in their July 14,
14, 2003 Form 10-Q, and October 28, 2003 press release as important in their decision making and
would have viewed these misrepresented facts as significantly altering the total mix of information
made available about Gilead from both a quantitative and qualitative standpoint. Had Plaintiffs, and
the other members of the Class, and the marketplace known of Gilead’s true financial condition and
business prospects, Plaintiffs and other members of the Class would not have purchased or otherwise
acquired their Gilead securities, or, if they had acquired such securities during the Class Period, they
would not have done so at the artificially inflated prices which they paid.

267. The market for Gilead’s publicly traded securities was open, well-developed, and
efficient at all relevant times. As a result of Defendants’ materially false and misleading statements,
Gilead’s publicly traded securities traded at artificially inflated prices during the Class Period.
Plaintiffs and other members of the Class purchased or otherwise acquired Gilead publicly traded
securities relying upon the integrity of the market price of Gilead’s publicly traded securities and
market information relating to Gilead, and have been damaged thereby, as evidenced by, among
others, the stock price decline on or about October 28, 2003 when artificial inflation was released from Gilead stock.

268. At all relevant times, the material misrepresentations particularized in this Complaint directly or proximately caused or were a substantial contributing cause of the damages sustained by Plaintiffs and other members of the Class. As described herein, during the Class Period, Defendants made or caused to be made a series of materially false or misleading statements about Gilead’s sales, business, product marketing and promotion, prospects, operations and financial results. These material misstatements had the cause and effect of creating in the market an unrealistically positive assessment of Gilead and its sales, products, business, and operations and financial results, thus causing the Company’s publicly traded securities to be overvalued and artificially inflated at all relevant times. Defendants’ materially false and misleading statements during the Class Period resulted in Plaintiffs and other members of the Class purchasing the Company’s publicly traded securities at artificially inflated prices, thus causing the damages complained of herein, as evidenced by, among others, the stock price decline on or about October 28, 2003 when artificial inflation was released from Gilead stock.

ADDITIONAL SCIENTER ALLEGATIONS

269. As alleged herein, Defendants acted with scienter in that they knew or disregarded with deliberate recklessness that the public documents and statements, issued or disseminated in the name of the Company, were materially false and misleading; knew that such statements or documents would be issued or disseminated to the investing public; and knowingly and substantially participated or acquiesced in the issuance or dissemination of such statements or documents as primary violations of the federal securities laws. As set forth elsewhere herein in detail throughout this complaint, Defendants, by virtue of their receipt of information reflecting the true facts regarding Gilead, their control over, and/or receipt and/or modification of Gilead’s allegedly materially misleading misstatements and/or their associations with the Company which made them privy to confidential proprietary information concerning Gilead, participated in the fraudulent scheme alleged herein.
270. Defendants knew and/or disregarded with deliberate recklessness the falsity and misleading nature of the information that they caused to be disseminated to the investing public. The ongoing fraudulent scheme described in this complaint could not have been perpetrated over a substantial period of time, as has occurred, without the knowledge and complicity of the personnel at the highest level of the Company, including each of the Individual Defendants.

271. In addition to the foregoing and other facts alleged herein, the following facts provide compelling evidence that Defendants acted with intent to deceive Gilead investors.

272. Importantly, the Individual Defendants were motivated to perpetuate the fraudulent scheme and course of conduct described herein so that they could sell their personally-held shares for gross proceeds of over $20 million at artificially inflated prices.\(^7\)

273. Within days after rebutting a Wall Street analyst’s concerns regarding inventory overstocking (implying strong demand for Viread) and receiving their second FDA warning letter, Defendants began to unload their Gilead shares throughout the month of August.

274. Notwithstanding their access to this and other non-public information, Defendants disposed of the following amounts of their stock:

**John C. Martin, President and CEO:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Number of Shares Sold</th>
<th>Price Per Share</th>
<th>Total Value</th>
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<tr>
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<td>TOTAL</td>
<td>50,000 (13.86% of stock and exercised options)</td>
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\(^7\) In the Court’s Amended Order Granting Defendants’ 12(b)(6) Motion to Dismiss the Consolidated Complaint, the Court ruled that Defendants’ sales in and of themselves do not show scienter. Figures outlining Defendants’ sales are included here because when the Complaint is viewed in its entirety, Defendants’ sales further support the strong inference of scienter raised in the Complaint and such sales also provide important context from which to view Defendants’ fraudulent scheme.
**Mark L. Perry, Executive Vice President, Operations**

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<td>5,000</td>
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52,344 (17.91% on 08/05/2003 and 4.90% on 08/06/2003 of stock and exercised options) $3,376,295

**John F. Milligan, Senior Vice President and CFO:**

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11,000 (20% of Stock and exercised options) $695,930

**Norbert W. Bischofberger, Executive Vice President, Research & Development:**

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**TOTAL:** 90,020 (23.21% on 08/05/2003 and 16.12% on 08/28/2003 of stock and exercised options)

$5,675,379.80

Anthony Carraciolo, Senior Vice President, Manufacturing:

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William A. Lee, Senior Vice President, Research:

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275. Both the timing of the sales and the sale prices are suspicious. First, all of the Individual Defendants’ sales occurred in succession over a twenty-four day period when they were misrepresenting the Company’s Viread sales figures and ignoring the impact that would result from the FDA’s Warning Letter which sought to curtail Gilead’s false and misleading promotion of Viread. This is the first and only time that all of the Individual Defendants sold Gilead shares during such a short period of time.

276. Second, contrary to what Gilead disclosed in its Second Quarter 2003 Form 10 Q, the FDA Warning Letter was issued on July 29, 2003, not August 7, 2003. See Exhibit F. Rather, the FDA Warning Letter was made public on August 7, 2003. The public disclosure of the letter shines a bright light on the Individual Defendants’ suspicious sales timing. Specifically, Defendants Perry and Bischofberger sold more than $3,000,000 worth of stock each between the date the FDA issued the FDA Warning Letter and the date it became public. Following suit, Defendant Martin sold more than $3,000,000 worth of stock on August 8, 2003. Third, and equally troubling, the Individual

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8 There was insufficient information in Defendant Carraciolo’s Form 4 filings with the SEC to allow Lead Plaintiffs to calculate what percentage of stock and exercised options Defendant Carraciolo sold during the Class Period. However, it is known that Defendant Carraciolo never sold any stock prior to the Class Period.
Defendants sold their shares between $61.17 to $66.10 per share, near the stock's peak at $70.61 and prior to a low of $50.27 on October 29, 2003.

277. Additionally, the Individual Defendants' prior trading history indicates that sales during the Class Period were both unusual and suspicious. In no time prior to the Class Period had all of the Individual Defendants ever sold stock during the same month. In fact, Defendant Carraciolo never sold a single share of Gilead stock prior to the Class Period. However, during a twenty-four day period in August 2003 the Individuals Defendants all sold significant amounts of stock near the height of Gilead's artificially inflated share price for proceeds of more than $20 million.

278. The Individual Defendants' knowledge about the false and misleading promotion of Viread, as evidenced by the Untitled FDA Letter and the FDA Warning Letter, as well as their false and misleading statements concerning sales of Viread during Second Quarter 2003, highlight the unusual nature of Defendants' conspicuously well-timed stock sales.

279. The unusual circumstances surrounding the Individual Defendants' sales of their stock during a 24-day period in August of 2003 further demonstrate both the Individual Defendants' motive to commit the fraud alleged herein as well as their scienter. As described herein, Defendants acted with scienter in that they knew, or with deliberate recklessness disregarded, that the public documents and statements issued or disseminated in the name of the Company were materially false and misleading; knew, or with deliberate recklessness disregarded, that such statements or documents would be issued or disseminated to the investing public; and knowingly and substantially participated or acquiesced in the issuance or dissemination of such statements or documents as primary violations of the federal securities laws. As set forth elsewhere herein in detail, the Individual Defendants, by virtue of their receipt of information reflecting the true facts regarding Gilead, their control over, and/or receipt and/or modification of Gilead's allegedly materially misleading misstatements and/or their associations with the Company which made them privy to confidential proprietary information concerning Gilead, participated in the fraudulent scheme alleged herein.
APPLICABILITY OF PRESUMPTION OF RELIANCE:
FRAUD-ON-THE-MARKET DOCTRINE

280. At all relevant times, the market for Gilead’s publicly traded securities was an efficient market for the following reasons, among others:

(a) Gilead’s securities met the requirements for listing, and were listed and actively traded on the NASDAQ, a highly efficient and automated market;

(b) as a regulated issuer, Gilead filed periodic public reports with the SEC, including reports on Form S-3;

(c) Gilead regularly communicated with public investors via established market communication mechanisms, including through regular disseminations of press releases on the national circuits of major newswire services and through other wide-ranging public disclosures, such as communications with the financial press and other similar reporting services; and

(d) Gilead was followed by several securities analysts employed by major brokerage firms who wrote reports that were distributed to the sales force and certain customers of their respective brokerage firms. Each of these reports was publicly available and entered the public marketplace.

281. As a result, the market for Gilead’s publicly traded securities promptly digested current information regarding Gilead from all publicly-available sources and reflected such information in Gilead’s securities prices. Under these circumstances, all purchasers of Gilead’s publicly traded securities during the Class Period suffered similar injury through their purchase of Gilead’s publicly traded securities at artificially inflated prices and a presumption of reliance applies.

NO SAFE HARBOR

282. The federal statutory safe harbor provided for forward-looking statements under certain circumstances does not apply to any of the allegedly false statements pleaded in this Complaint. Many of the specific statements pleaded herein were not identified as “forward-looking statements” when made. To the extent there were any forward-looking statements, there were no meaningful cautionary statements identifying important factors that could cause actual results to differ materially from those in the purportedly forward-looking statements. Alternatively, to the
extent that the statutory safe harbor does apply to any forward-looking statements pleaded herein, Defendants are liable for those false forward-looking statements because at the time each of those forward-looking statements was made, the particular speaker knew that the particular forward-looking statement was false, and/or the forward-looking statement was authorized and/or approved by an executive officer of Gilead who knew that those statements were false when made. Moreover, to the extent that Defendants issued any disclosures designed to “warn” or “caution” investors of certain “risks,” those disclosures were also false and misleading since they did not disclose that Defendants were actually engaging in the very actions about which they purportedly warned and/or had actual knowledge of material adverse facts undermining such disclosures.

COUNT I

FOR VIOLATIONS OF SECTION 10(b) OF THE EXCHANGE ACT AND RULE 10b-5 PROMULGATED THEREUNDER AGAINST ALL DEFENDANTS

283. Plaintiffs repeat and reallege the allegations set forth above as though fully set forth herein. This claim is asserted against all Defendants.

284. During the Class Period, Gilead and the Individual Defendants, and each of them, carried out a plan, scheme and course of conduct which was intended to and, throughout the Class Period, did: (i) deceive the investing public, Plaintiffs and other Class members, as alleged herein; (ii) artificially inflate and maintain the market price of Gilead’s publicly traded securities; and (iii) cause Plaintiffs and other members of the Class to purchase Gilead’s publicly traded securities at artificially inflated prices. In furtherance of this unlawful scheme, plan and course of conduct, Gilead and the Individual Defendants, and each of them, took the actions set forth herein.

285. These Defendants: (i) employed devices, schemes, and artifices to defraud; (ii) made untrue statements of material fact and/or omitted to state material facts necessary to make the statements not misleading; and (iii) engaged in acts, practices, and a course of business which operated as a fraud and deceit upon the purchasers of the Company's securities in an effort to maintain artificially high market prices for Gilead's securities in violation of Section 10(b) of the Exchange Act and Rule 10b-5. These Defendants are sued as primary participants in the wrongful
and illegal conduct charged herein. The Individual Defendants are also sued as controlling persons of Gilead, as alleged below.

286. In addition to the duties of full disclosure imposed on Defendants as a result of their making of affirmative statements and reports, or participating in the making of affirmative statements and reports to the investing public, they each had a duty to promptly disseminate truthful information that would be material to investors in compliance with the integrated disclosure provisions of the SEC as embodied in SEC Regulation S-X (17 C.F.R. § 210.01 et seq.) and S-K (17 C.F.R. §229.10 et seq.) and other SEC regulations, including accurate and truthful information with respect to the Company's operations, sales, product marketing and promotion, financial condition and operational performance so that the market prices of the Company's publicly traded securities would be based on truthful, complete and accurate information.

287. Gilead and each of the Individual Defendants, individually and in concert, directly and indirectly, by the use, means or instrumentalities of interstate commerce and/or of the mails, engaged and participated in a continuous course of conduct to conceal adverse material information about the business, business practices, sales performance, product marketing and promotion, operations and future prospects of Gilead as specified herein.

288. These Defendants each employed devices, schemes and artifices to defraud, while in possession of material adverse non-public information and engaged in acts, practices, and a course of conduct as alleged herein in an effort to assure investors of Gilead's value and performance and continued substantial sales, financial and operational growth, which included the making of, or the participation in the making of, untrue statements of material facts and omitting to state material facts necessary in order to make the statements made about Gilead and its business operations and future prospects in the light of the circumstances under which they were made, not misleading, as set forth more particularly herein, and engaged in transactions, practices and a course of business which operated as a fraud and deceit upon the purchasers of Gilead's securities during the Class Period.

289. Each of the Individual Defendants' primary liability, and controlling person liability, arises from the following facts: a) each of the Individual Defendants was a high-level executive and/or director at the Company during the Class Period; b) each of the Individual Defendants, by
virtue of his responsibilities and activities as a senior executive officer and/or director of the
Company, was privy to and participated in the creation, development and reporting of the Company's
internal sales and marketing plans, projections and/or reports; c) each of the Individual Defendants
enjoyed significant personal contact and familiarity with each other and were advised of and had
access to other members of the Company's management team, internal reports, and other data and
information about the Company's financial condition and performance at all relevant times; and d) each of the Individual Defendants was aware of the Company's dissemination of information to the
investing public which each knew or recklessly disregarded was materially false and misleading.

290. Each of these Defendants had actual knowledge of the misrepresentations and
omissions of material facts set forth herein, or acted with deliberately reckless disregard for the truth
in that each failed to ascertain and to disclose such facts, even though such facts were available to
each of them. Such Defendants' material misrepresentations and/or omissions were done knowingly
or with deliberate recklessness and for the purpose and effect of concealing Gilead's operating
condition, sales, product marketing and promotional practices and future business prospects from the
investing public and supporting the artificially inflated price of its securities. As demonstrated by
Defendants' overstatements and misstatements of the Company's financial condition and
performance throughout the Class Period, each of the Individual Defendants, if he did not have
actual knowledge of the misrepresentations and omissions alleged, was reckless in failing to obtain
such knowledge by deliberately refraining from taking those steps necessary to discover whether
those statements were false or misleading.

291. As a result of the dissemination of the materially false and misleading information
and failure to disclose material facts, as set forth above, the market prices of Gilead's securities were
artificially inflated during the Class Period. In ignorance of the fact that market prices of Gilead's
publicly traded securities were artificially inflated, and relying directly or indirectly on the false and
misleading statements made by Defendants, or upon the integrity of the market in which the
securities trade, and/or on the absence of material adverse information that was known to or
disregarded with deliberate recklessness by Defendants but not disclosed in public statements by
Defendants during the Class Period, Plaintiffs and the other members of the Class acquired Gilead
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securities during the Class Period at artificially high prices and were damaged thereby, as evidenced by, among others, the stock price decline on or about October 28, 2003 when artificial inflation was released from Gilead stock.

292. At the time of said misrepresentations and omissions, Plaintiffs and other members of the Class were ignorant of their falsity, and believed them to be true. Had Plaintiffs and the other members of the Class and the marketplace known of the true performance, sales, marketing, promotion and other fraudulent business practices, future prospects and intrinsic value of Gilead, which were not disclosed by Defendants, Plaintiffs and other members of the Class would not have purchased or otherwise acquired their Gilead publicly traded securities during the Class Period, or, if they had acquired such securities during the Class Period, they would not have done so at the artificially inflated prices which they paid.

293. By virtue of the foregoing, Gilead and the Individual Defendants have each violated Section 10(b) of the Exchange Act, and Rule 10b-5 promulgated thereunder.

294. As a direct and proximate result of Defendants' wrongful conduct, Plaintiffs and the other members of the Class suffered damages in connection with their respective purchases and sales of the Company's securities during the Class Period, as evidenced by, among others, the stock price decline on or about October 28, 2003 when artificial inflation was released from Gilead stock.

COUNT II

FOR VIOLATIONS OF SECTION 20(A) OF THE EXCHANGE ACT AGAINST THE INDIVIDUAL DEFENDANTS

295. Plaintiffs repeat and reiterate the allegations as set forth above as if set forth fully herein. This claim is asserted against the Individual Defendants.

296. Each of the Individual Defendants acted as a controlling person of Gilead within the meaning of Section 20(a) of the Exchange Act as alleged herein. By virtue of their high-level positions with the Company, participation in and/or awareness of the Company's operations and/or intimate knowledge of the Company's fraudulent marketing and promotions and actual performance, each of the Individual Defendants had the power to influence and control and did influence and control, directly or indirectly, the decision-making of the Company, including the content and
dissemination of the various statements which Plaintiffs contend are false and misleading. Each of
the Individual Defendants was provided with or had unlimited access to copies of the Company's
reports, press releases, public filings and other statements alleged by Plaintiffs to be misleading prior
to and/or shortly after these statements were issued and had the ability to prevent the issuance of the
statements or cause the statements to be corrected.

297. In addition, each of the Individual Defendants had direct involvement in the day-to-
day operations of the Company and, therefore, is presumed to have had the power to control or
influence the particular transactions giving rise to the securities violations as alleged herein, and
exercised the same.

298. As set forth above, Gilead and the Individual Defendants each violated Section 10(b)
and Rule 10b-5 by their acts and omissions as alleged in this Complaint. By virtue of their
controlling positions, each of the Individual Defendants is liable pursuant to Section 20(a) of the
Exchange Act. As a direct and proximate result of Defendants' wrongful conduct, Plaintiffs and
other members of the Class suffered damages in connection with their purchases of the Company's
securities during the Class Period, as evidenced by, among others, the stock price decline on or about
October 28, 2003 when artificial inflation was released from Gilead stock.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs, on their own behalf and on behalf of the Class, pray for relief and
judgment, as follows:

A. Declaring that this action is a proper class action, and certifying Plaintiffs as class
representatives pursuant to Rule 23 of the Federal Rules of Civil Procedure and Plaintiffs' counsel as
Lead Counsel for proposed Class;

B. Awarding compensatory damages in favor of Plaintiffs and the other Class members
against all Defendants, jointly and severally, for all damages sustained as a result of Defendants''
wrongdoing, in an amount to be proven at trial, including interest thereon;

C. Awarding Plaintiffs and the Class their reasonable costs and expenses incurred in this
action, including counsel fees and expert fees; and

D. Such other and further relief as the Court deems appropriate.
JURY TRIAL DEMANDED

Plaintiffs hereby demand a trial by jury.

DATED: July 10, 2009

KAPLAN FOX & KILSHEIMER LLP

/s/ LAURENCE D. KING

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Co-Lead Counsel for Plaintiffs
PROOF OF SERVICE

I, Adrianna D. Gutierrez, declare that I am over the age of eighteen (18) and not a party to the within action. I am employed in the law firm of Kaplan Fox & Kilheimer LLP, 350 Sansome Street, Suite 400, San Francisco, California 94111.

On July 10, 2009, I used the Northern District of California’s Electronic Case Filing System, with the ECF registered to Laurence D. King to file the following document(s):

FIFTH CONSOLIDATED AMENDED CLASS ACTION COMPLAINT FOR VIOLATION OF FEDERAL SECURITIES LAWS

The ECF system is designed to send an e-mail message to all parties in the case, which constitutes service. The parties served by e-mail in this case are found on the Court’s Electronic Mail Notice List.

On this date, I served the below parties:

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<tr>
<td>ABRAHAM FRUCHTER &amp; TWERSKY LLP</td>
<td>JIGARJIAN LAW OFFICE</td>
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<td>128 Tunstead Avenue</td>
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<tr>
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I declare under penalty of perjury under the laws of the United States of America and the State of California that the foregoing is true and correct.

Executed July 10, 2009, at San Francisco, California.

Adrianna D. Gutierrez
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EXHIBIT B
GILEAD
SCIENCES

FDA Advisory Committee Briefing Document

Viread™
(Tenofovir DF)

For the Treatment of HIV-1 Infection in Adults
in Combination with Other Antiretroviral Agents

NDA 21-356

Applicant:
Gilead Sciences, Inc.
333 Lakeside Dr.
Foster City, CA 94404
USA

Phone: (650) 574-3000
Fax: (650) 522-5489

Date of Document: 30 August 2001

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION
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1. SUMMARY

Despite improvements in morbidity and mortality, a substantial number of patients do not achieve adequate suppression of HIV viral replication with available antiretroviral therapies. Drug intolerance, inadequate adherence to the prescribed regimen, pharmacokinetic or pharmacodynamic drug interactions, and the emergence of resistant strains have each been implicated as reasons that patients either fail to achieve or experience a loss of virologic control. New therapeutic options are needed that provide durable anti-HIV activity, are well-tolerated, and contribute to improvements in the quality of life for patients infected with HIV. In particular, there is a need for new therapies for patients who have failed multiple regimens. While recognizing the difficulties associated with the development of drugs for this segment of the patient population, community representatives, their caregivers, and regulatory authorities, including the Division of Antiviral Drugs have encouraged sponsors to include treatment-experienced patients in their drug development programs.

Tenofovir is a novel nucleotide analog with activity against human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2) and hepatitis B virus. Tenofovir diphosphate (PMPApp), the active intracellular moiety, is a potent inhibitor of retroviral reverse transcriptase and acts as a DNA chain terminator.

During preclinical evaluation, tenofovir demonstrated low oral bioavailability. An orally available prodrug of tenofovir, tenofovir disoproxil fumarate (DF), was selected for clinical development because of its advantageous pharmacokinetic profile, oral bioavailability, potent antiviral activity, and unique in vitro resistance profile.

Clinical development of tenofovir DF was initiated in 1997, leading to submission of a New Drug Application (NDA) in May 2001. Tenofovir DF was submitted for accelerated approval based on surrogate efficacy as well as safety endpoints from 24-week data; along with safety data from extended dosing phases of the registrational studies, wherein patients have been treated for a mean of 58 weeks with some patients having received tenofovir DF for up to 143 weeks. The application is based on the overall evidence accumulated in adequate and well-controlled studies demonstrating the efficacy and safety of tenofovir DF for treatment-experienced HIV-infected patients.

The NDA for tenofovir DF includes data from nearly 1,050 HIV-infected patients who have been enrolled and treated in clinical studies evaluating safety, pharmacokinetics, and antiviral activity. Clinical studies have been complemented by extensive genotypic and phenotypic assessment of clinical HIV isolates. The results demonstrate that tenofovir DF taken once daily has an excellent safety profile and significant anti-HIV activity, including activity against multi-drug resistant HIV.

Pivotal clinical studies reported in the NDA focused on HIV-infected adults receiving various combinations of the available anti-HIV drugs (studies 902 and 907). Additional studies evaluated pharmacokinetics and bioequivalence (studies 901, 909, and 914) and...
safety (study 908). A 96-week study (study 903) designed to support traditional approval is currently underway to evaluate the safety and efficacy of tenofovir DF in treatment-naïve patients. Results from the initial 48 weeks of study 903 will be available in Spring 2002. A second confirmatory study (study 928) will be conducted in treatment-experienced pediatric patients.

Expanded access programs are ongoing in several countries and have enrolled 3,880 patients as of 27 August 2001, including 2,214 in the U.S.
2. INTRODUCTION

Tenofovir disoproxil fumarate (9-[(R)-2-[[bis[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl] adenine fumarate 1:1, tenofovir DF) is an orally bioavailable ester prodrug of tenofovir (also known as PMPA), an acyclic nucleotide analog with activity in vitro against retroviruses, including HIV-1, HIV-2, and hepatitis B virus (HBV). Due to the presence of a phosphonate group, tenofovir is negatively charged at neutral pH, which limits its oral bioavailability. Following absorption, tenofovir DF is rapidly converted to tenofovir which is metabolized intracellularly to the active metabolite, tenofovir diphosphate, a competitive inhibitor of HIV-1 reverse transcriptase (RT) that terminates the growing DNA chain.

Acyclic phosphonomethylether nucleosides like tenofovir exhibit distinct biological properties. Due to their efficient intracellular activation to their active metabolites, they possess potent antiviral activity in vivo. Also, the parent compounds and their metabolites have a prolonged intracellular half-life, which allows for infrequent administration. Finally, induction of antiretroviral resistance to these compounds in vitro has been difficult, possibly as a result of their minimal structure and similarity to the natural substrate (dATP).

Rationale for Development of Tenofovir DF

Despite the availability of potent antiretroviral agents, some patients do not achieve or are unable to maintain a viral load below the limit of assays used in clinical practice (i.e., plasma HIV-1 RNA levels < 400 or < 50 copies/mL). It is likely that many of these virological failures are due to the development of drug resistance or to re-emergence of HIV-1 with pre-existing resistance mutations. Incomplete suppression of virus allows continued replication, particularly of strains with reduced sensitivity to the antiretroviral agents being used, thus putting these patients at increased risk for disease progression or death.\(^1\)\(^2\) Since the development of resistance to the NRTI, NNRTI, and PI components of anti-HIV-1 regimen is a significant problem in achieving long-term, sustained viral suppression, antiretroviral agents that are less prone to resistance development and that maintain activity in the presence of pre-existing mutations are urgently needed. Clinical data in both treatment-naïve and treatment-experienced HIV-1-infected patients demonstrate that tenofovir DF has a unique HIV resistance profile that will satisfy these requirements. In particular, tenofovir DF exhibits activity against viruses displaying mutations with reduced sensitivity to other nucleoside analogs and only rarely selects for virus mutations.

In addition to its unique resistance profile, tenofovir DF meets other desirable requirements of a new antiretroviral agent. Tenofovir DF is a potent agent that is synergistic or additive when combined with all antiretroviral agents inhibiting the same or different aspects of viral replication. Tenofovir DF is administered on a once daily dosing schedule, an important requirement for simplifying treatment regimens and improving adherence. The long intracellular half-life means that delay in dosing would prevent a significant fall in drug level and rebound in viral replication. Finally, no evidence of clinically significant tenofovir DF-
related toxicity has been demonstrated in treatment-experienced and treatment-naïve HIV-infected patients.

Overview of Clinical Development Program

Gilead Sciences has undertaken a clinical program to investigate the antiviral activity of tenofovir DF, either as monotherapy or in combination with a variety of other antiretroviral agents, in antiretroviral treatment-naïve and treatment-experienced HIV-infected patients.

The primary focus of the NDA submission and Safety Update is on the data from four clinical studies of oral tenofovir DF in HIV-infected patients: studies 901, 902, 907, and 908. These studies involve approximately 1,050 patients who received tenofovir DF alone (study 901) or in combination with other antiretroviral agents (studies 902, 907, 908, and 910). Pharmacokinetic data are also presented from two studies in healthy volunteers (studies 909 and 914). As background, data are also included from a phase 1 study of intravenous tenofovir (study 701).

Table 2-1 summarizes the completed and ongoing studies in the tenofovir DF development program.
Table 2-1. Summary of Tenofovir/Tenofovir DF Clinical Development Program

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Patient Population</th>
<th>Initial Dose(s) (mg per day)</th>
<th>Enrolled/Target</th>
<th>Location</th>
<th>Status (as of 01 August 2001)</th>
</tr>
</thead>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 1/2 Studies in HIV-Infected Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>701</td>
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<td>1 mg/kg, 3 mg/kg (IV)*</td>
<td>20/40</td>
<td>US</td>
<td>Complete</td>
</tr>
<tr>
<td>901</td>
<td>Naive and Experienced</td>
<td>75, 150, 300, 600 mg</td>
<td>59/50</td>
<td>US</td>
<td>Complete**</td>
</tr>
<tr>
<td>917</td>
<td>Naive</td>
<td>300 mg</td>
<td>8/18</td>
<td>US</td>
<td>Enrollment ongoing</td>
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<tr>
<td>Phase 2/3 Studies in HIV-Infected Patients</td>
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<td>Experienced</td>
<td>75, 150, 300 mg</td>
<td>189/175</td>
<td>US</td>
<td>Complete**</td>
</tr>
<tr>
<td>907</td>
<td>Experienced</td>
<td>300 mg</td>
<td>552/600</td>
<td>US, Europe, Australia</td>
<td>Complete**</td>
</tr>
<tr>
<td>903</td>
<td>Naive</td>
<td>300 mg</td>
<td>601/600</td>
<td>US, Europe, South America</td>
<td>Enrollment complete; study ongoing.</td>
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<tr>
<td>Open-Label Safety Studies</td>
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</tr>
<tr>
<td>908</td>
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<td>300 mg</td>
<td>296/300</td>
<td>US</td>
<td>Enrollment complete study ongoing.</td>
</tr>
<tr>
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<td>300 mg</td>
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<td>Phase 1 Pharmacokinetic Studies in Healthy Volunteers</td>
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<td>Expanded Access Program</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>Not applicable</td>
<td>US, Europe, and Canada, Australia</td>
<td>Enrollment ongoing</td>
</tr>
</tbody>
</table>

* Study 701 involved tenofovir given intravenously
** A rollover protocol (study 910) was made available in October 2000 for patients in studies 901, 902, and 907 remaining on tenofovir DF beyond 48 weeks of treatment.
3. PRECLINICAL SUMMARY

The antiviral activity of tenofovir has been demonstrated using in vitro assays and in vivo animal models, including SIV infected macaques. Toxicology studies were conducted in rats and dogs with tenofovir administered by the intravenous (iv) route to support initial clinical studies in which tenofovir was administered iv. The major target organs of toxicity identified in these short term studies were kidney, gastrointestinal tract, and bone.

The definitive preclinical ADME and toxicology studies for this compound were conducted using tenofovir DF administered orally. The bioavailability and pharmacokinetic profile of tenofovir DF have been studied in mice, rats, dogs and rhesus monkeys. Acute, subchronic and/or chronic toxicology studies of tenofovir DF have been conducted in mice, rats and dogs. Rhesus monkeys have been used to further define the acute and subchronic toxicologic effects of tenofovir DF. Long-term carcinogenicity studies in rats and mice are in progress.

3.1. Mechanism of Action

Tenofovir is taken up by cells and undergoes phosphorylation to the antivirally active metabolite PMPApp. PMPApp competitively inhibits both RNA- and DNA-directed reverse transcriptase activity. PMPApp competes with deoxyadenosine triphosphate (dATP) for incorporation into nascent DNA and, since it lacks a 3' hydroxyl group, causes premature chain termination. The Ki for reverse transcription (RNA-directed DNA synthesis) is 0.02 µM, more than 200-fold lower than the Ki for human DNA polymerase α, and more than 3,000-fold lower than the Ki values for β and γ. Generally, the lowest incorporation efficiencies with all three polymerases (α, β, and γ) were found for PMPApp when compared to ddATP, ddCTP, 3TCTP, d4TTP, or PMEGpp.

3.2. In Vitro Cytotoxicity

The cytotoxicity of tenofovir was determined both in quiescent and activated peripheral blood mononuclear cells (PBMCs) and in an established T-lymphocytic MT-2 cell line. In PBMCs and MT-2 cells, tenofovir exhibited low cytotoxicity with CC50 values > 1 mM. In quiescent PBMCs, no cytotoxic effect of tenofovir was detected at concentrations as high as 100 µM.

3.3. Preclinical Evaluation of Antiviral Activity

Tenofovir and tenofovir DF were evaluated in vitro for antiviral activity (IC50) and cytotoxicity (CC50) in HIV-1 IIIb and clinical strain 96-250 in MT-2 cells, peripheral blood mononuclear cells (PBMCs), or a macrophage/dendritic cell coculture. The selectivity index (SI = CC50/IC50) for tenofovir was > 2,000. Due to its increased cellular permeability, the anti-HIV activity of tenofovir DF is increased by 17- to 90-fold over tenofovir.
Tenofovir Disoproxil Fumarate
FDA Briefing Document
NDA 21-356

The concentration of tenofovir required for 50% inhibition (IC$_{50}$) of wild-type HIV-1 is 1-6 µM in MT-2 or MT-4 cells (based on inhibition of viral cytopathic effect) and 0.2-0.6 µM in PBMCs (based on inhibition of virus production). The activity of tenofovir against clinical HIV-1 isolates from non-B subtypes has also been studied. The mean IC$_{50}$ values for tenofovir against HIV-1 subtypes A, C, D, E, F, G, and O in primary PBMC cultures were all within twofold of the subtype B IC$_{50}$ value (range: 0.55 to 2.2 µM). Tenofovir has also been shown to be active in vitro against HIV-2, with similar potency as observed against HIV-1 (IC$_{50}$ of 4.9 µM in MT-4 cells).

Tenofovir, paired individually with 14 other antiretroviral compounds, was tested for additive, antagonistic, or synergistic antiviral activity against HIV-1 in MT-2 cells. Tenofovir showed minor to moderate synergy with ddI and nelfinavir, and strong synergy with ZDV, amprenavir, and all non-nucleoside reverse transcriptase inhibitors (NNRTIs) tested. The other combinations were additive, and no significant antiviral antagonism was observed. Combinations of tenofovir and 50 µM hydroxyurea show greater than a 26-fold decrease in the tenofovir IC$_{50}$ value for the wild-type HIV molecular clone NL4-3. Notably, HIV isolates with RT mutations associated with slightly decreased susceptibility to tenofovir show hypersusceptibility to tenofovir in the presence of hydroxyurea. However, this synergy was not demonstrated in vivo in study 901.

The in vivo antiviral activity of tenofovir (sc) was demonstrated in murine, feline and primate models. Tenofovir DF (po) and tenofovir (sc) had comparable activity in murine sarcoma virus- (MSV)-infected severe combined immunodeficient mouse model (SCID mice); orally administered tenofovir had no effect, consistent with its poor oral bioavailability. In studies of acute and chronic FIV infection in cats, tenofovir (30 mg/kg/day) reduced circulating viral FIV RNA but not PBMC-associated, co-culture-detected virus burden. In a study of SIV-infected juvenile macaques, tenofovir (30 or 75 mg/kg/day) was more efficacious than zidovudine (100 mg/kg/day) as assessed by surrogate markers of SIV infection and clinical status. In further studies in SIV-infected rhesus macaques, tenofovir DF was effective in preventing infection, reducing viral load and slowing progression of disease, maintaining long term (> 2 year) efficacy, and producing clinical benefit in the presence of partially resistant strains of virus.

### 3.3.1. Anti-Hepatitis B (HBV) Activity

Tenofovir is a potent and selective inhibitor of HBV in vitro. Tenofovir inhibits HBV production in HepG2 2.2.15 and HB611 cells with IC$_{50}$ values of 1.1 and 2.5 µM, respectively, and corresponding CC$_{50}$ values of > 100 and 260 µM, respectively. As observed with anti-HIV activity, tenofovir DF showed increased in vitro potency against HBV in comparison with tenofovir. Tenofovir was also shown to be equally effective against both wild-type and lamivudine-resistant HBV in a cell culture assay. In contrast, lamivudine demonstrated > 200-fold reduced activity against this HBV mutant. Tenofovir has also been shown to inhibit the replication of duck HBV (DHBV) in primary duck hepatocytes with an IC$_{50}$ of 0.11 µM.
3.4. Mitochondrial Toxicity

A variety of clinical symptoms observed in HIV patients treated with prolonged NRTI therapy may be linked to mitochondrial toxicity. These include myopathy and cardiomyopathy, polyneuropathy, lactic acidosis, pancreatitis, lipodystrophy and possibly others. Tenofovir DF was compared with nucleoside reverse transcriptase inhibitors (NRTIs) for effects on mitochondrial DNA (mtDNA) synthesis and lactic acid production.

In HepG2 human liver cells, tenofovir DF (3-300 µM), lamivudine and abacavir had no effect on mitochondrial DNA content, zidovudine and stavudine caused 30-40% reduction, and ddC and ddi caused marked depletion of mtDNA.22 In normal human skeletal muscle cells (proliferating or quiescent), tenofovir DF (300 µM), lamivudine, abacavir and zidovudine had no effect on mtDNA levels, stavudine caused moderate reduction, and ddC and ddi showed marked depletion of mtDNA.22

Tenofovir DF and lamivudine did not increase the lactic acid production in HepG2 cells and skeletal muscle cells relative to the untreated control, whereas zidovudine produced a concentration-dependent increase in the lactate production in both cell types tested.22 Results of these in vitro studies suggest a low potential of tenofovir DF to interfere with mitochondrial functions.

In vivo, no evidence of mitochondrial-related hepatic, hematologic, cardiac, pancreatic, or skeletal muscle toxicity was detected in chronic toxicity studies (42-week) in rats and dogs.23, 24

3.5. Nonclinical Pharmacology and Toxicology

The nonclinical safety profile of adefovir dipivoxil has been extensively evaluated in pharmacokinetic/ADME, pharmacology, and toxicology studies using test systems and protocols accepted by the ICH and international health authorities. This evaluation has included studies in mice, rats, guinea pigs, rabbits, dogs, and monkeys. The principal target organs of toxicity following oral administration of tenofovir DF or subcutaneous administration of tenofovir in animal models were the gastrointestinal tract, kidneys and bone. Nephrotoxicity was the primary dose-limiting toxicity associated with the oral administration of tenofovir DF in dogs and monkeys; gastrointestinal toxicity was dose-limiting in rats. Toxicity to bone was demonstrated to be secondary to dose-, species-, and age-related alterations in phosphate homeostasis, resulting from inhibition of intestinal phosphate absorption and/or renal phosphate reabsorption. Tenofovir had no adverse effects on fertility and reproductive performance, embryo-fetal development or peri- and postnatal development. Like marketed nucleoside analogue antivirals, in in vitro genetic toxicity studies, tenofovir DF induces chromosomal aberrations but not point mutations. Tenofovir was negative in the in vivo mouse micronucleus assay. Carcinogenicity studies are ongoing. In all species examined, tenofovir DF was hydrolyzed to tenofovir following absorption, and tenofovir was cleared exclusively by renal elimination, without further metabolic changes, by a combination of glomerular filtration and tubular secretion.
Conclusions from the nonclinical evaluations are as follows:

- Virology, pharmacology, pharmacokinetics, and toxicology studies provide scientific support for the potential safety and efficacy of tenofovir DF at the proposed human dose.

- The toxicity profile of tenofovir DF has been well characterized in animals and mechanisms of target organ toxicity are generally understood.

- Potential clinical adverse effects are reversible and easily monitored.

### 3.5.1. Safety Pharmacology

Single oral doses of tenofovir DF had no adverse effects on the central nervous system (male rats, 50 or 500 mg/kg) or on cardiovascular and respiratory function (conscious male dogs, 30 mg/kg). An assessment of effects on renal function demonstrated increased urinary electrolyte excretion and urine volume in rats administered tenofovir DF 500 mg/kg; no effect was observed at 50 mg/kg. When rats were administered tenofovir DF (0, 50, or 500 mg/kg) to evaluate effects on the gastrointestinal transit of a charcoal meal, there was reduced gastric emptying at 500 mg/kg/day, but no effect at 50 mg/kg/day.

### 3.5.2. Absorption, Distribution, Metabolism, and Excretion (ADME)

Following oral administration of tenofovir DF, maximum tenofovir plasma concentrations were reached within 0.25 to 1.5 hours and declined in a biphasic manner. The observed terminal half-life values were approximately 7, 9, and 60 hours in rats, monkeys, and dogs respectively. Due to the long terminal half-life in dogs, a substantial degree of accumulation was observed upon daily repeat dosing. The oral bioavailability of tenofovir DF was greatest in dogs and monkeys (30-40%) and least in rodents (10-20%). The prodrug moiety was efficiently cleaved in all species such that minimal intact prodrug was observed in systemic circulation. No circulating metabolites of tenofovir, other than the monoester, observed at early time points in rats and dogs, have been observed. This is consistent with the lack of metabolism of tenofovir in intestinal and liver homogenates. A small but statistically significant degree of CYP P450 induction (CYP 1A and 2B) was observed in livers from rats given tenofovir DF at doses of 400 mg/kg/day. Given the known differences in cytochrome P450 across species, the clinical relevance of this observation in humans is unknown. Extensive tissue distribution, suggested by the plasma pharmacokinetics of tenofovir, was confirmed in studies with 14C-labeled tenofovir in dogs and rats. Major sites of tissue uptake included the liver and kidney. Tenofovir was excreted (14-24% of plasma concentrations) but not concentrated in milk from lactating rats. Tenofovir was excreted unchanged in the urine of all animal species tested and renal excretion was identified as the primary route of elimination.
3.5.3. Target Organ Toxicity

The nonclinical toxicity of tenofovir DF was studied in mice, rats, rabbits, and dogs. Special studies to elucidate mechanisms of toxicity were conducted primarily in rats and monkeys. The target organs of toxicity identified in the preclinical program were the gastrointestinal tract, renal tubular epithelium, and bone.

3.5.3.1. Gastrointestinal Toxicity

Gastrointestinal (GI) toxicity, observed primarily in rats, was dose related, reversible, and characterized by inflammation of the stomach and intestines, epithelial cytomegaly in the duodenum and jejunum, and villous atrophy of the ileum in rodents. GI toxicity appeared to be related to high local concentrations in the GI tract of rats reflecting high doses evaluated in toxicology studies (100-1000 mg/kg/day) to compensate for the relatively low oral bioavailability of tenofovir DF in this species. Detection of toxicity to the gastrointestinal tract appeared to be inversely proportional to the length of the tenofovir DF administration period; this may represent an adaptation to the effects of the drug. Acute GI toxicity was observed in dogs administered tenofovir DF 180 mg/kg/day for 5 days; no GI toxicity was observed in dogs administered tenofovir DF chronically (30 mg/kg/day for 42 weeks). No GI toxicity occurred in monkeys administered tenofovir DF for 56 days at doses up to 50 mg/kg/day.

3.5.3.2. Nephrotoxicity

Renal tubular epithelial karyomegaly, a morphologic change without pathologic consequence, was the most sensitive histological indicator of an effect on the kidney and was observed in rats, dogs, and monkeys. In dogs, the species most sensitive to effects on the kidney, additional microscopic alterations reported following chronic administration of tenofovir DF (≥ 10 mg/kg/day for 42 weeks) included individual cell necrosis, tubular dilatation, degeneration/regeneration, pigment accumulation, and interstitial nephritis. Associated biochemical changes in dogs administered tenofovir DF 30 mg/kg/day were a slight elevation in serum creatinine, glucosuria, proteinuria, and increased urine volume. The incidence and severity of nephrotoxicity was dose related. Effects were reversible following cessation of treatment. In rats administered tenofovir DF 1000 mg/kg/day for 42 weeks, slight elevations in serum creatinine were observed; no biochemical or histopathologic evidence of nephrotoxicity was observed in rat at 300 mg/kg/day. Rhesus monkeys administered tenofovir DF at dose of 250 mg/kg/day or more developed biochemical and/or histopathologic evidence of nephrotoxicity; no nephrotoxicity was observed in monkeys at 30 mg/kg/day.

In vitro models for renal proximal tubular toxicity were used to investigate the in vivo differences in nephrotoxicity observed between the structurally related antiviral nucleotide analogues: tenofovir DF, adefovir dipivoxil (ADV), and cidofovir (CDV). Steady-state transport kinetic experiments in CHO cells stably expressing the functional human renal organic anion transporter 1 (hOAT1) revealed a similar transport efficiency (calculated as...
$V_{maa}/K_m$ ratio) for the three analogs. Clinical pharmacokinetic data indicate a similar rate of active tubular secretion for the three nucleotides. These observations suggest that a lack of interference with essential intracellular function(s) rather than a difference in renal transport and accumulation in proximal tubule cells is responsible for the improved nephrotoxicity profile of tenofovir DF compared to cidofovir and adefovir.

Tenofovir DF had minimal effect on the growth of primary human renal proximal tubular epithelial cells (RPTECs) (CC50 > 2 mM), long-term viability of quiescent RPTECs (0.5 mM), and integrity-differentiated proximal tubular epithelium formed by RPTECs (>3 mM). In contrast, CDV (0.5 mM) and ADV (0.3) reduced the half-life of quiescent RPTECs and reduced tubular epithelium integrity (CDV - 0.1 mM; ADV - 1.1 mM). Overall, these in vitro findings correlate with the in vivo nephrotoxicity potential of the three antiviral nucleotides and support the nonclinical and clinical observations of low nephrotoxic potential of tenofovir DF.

3.5.3.3. Bone

Chronic administrations of high doses of tenofovir (sc) or tenofovir DF (po) to immature animals resulted in reversible bone alterations ranging in severity from minimal decreases in bone mineral density and content (oral tenofovir DF: rats and dogs), to pathologic osteomalacia (subcutaneous tenofovir: monkeys). Effects were dose/exposure-, age-, and species-specific.

Osteomalacia was reported in juvenile rhesus monkeys administered tenofovir (30 mg/kg/day, sc; AUC = 25X humans at 300 mg/day) chronically in anti-SIV efficacy studies. Marked hypophosphatemia was seen in effected monkeys. Monkeys treated chronically with tenofovir (sc) 10 mg/kg/day (AUC = 5X humans), had no clinical or radiographic evidence of bone toxicity, and animals who were dose-reduced from 30 mg/kg/day to 10 mg/kg/day showed improvement in bone parameters.

Based on the findings in the SIV efficacy models, bone morphometry (peripheral quantitative computed tomography, pQCT) and biochemistry evaluations were added to ongoing chronic oral toxicity studies of tenofovir DF in rats and dogs (urinary markers of bone resorption were urinary calcium, deoxypyridinoline in rats and N-telopeptide in dogs; serum markers of bone formation were osteocalcin in rats and sALP in dogs). No gross or microscopic alterations in bone were observed in the chronic toxicity studies. Marginal to slight decreases in bone mineral density and content were seen by pQCT (distal femoral metaphyses and mid-femoral diaphyses) after 13 and 42 weeks of orally administered tenofovir DF in rats (300 - 1,000 mg/kg/day; AUC = 6X humans) and dogs (30 mg/kg/day; AUC = 10X humans). There was a dose related, slight to mild increase in urinary phosphate, marked increase in urinary calcium (high doses). Alterations in biochemical markers were increased deoxypyridinoline (rats) and N-telopeptide (dogs), and increased serum parathyroid hormone, osteocalcin (rats) and bone-alkaline phosphatase (dogs), suggesting increased bone turnover. All bone parameters showed a recovery following a treatment-free period.
In addition to specialized evaluations incorporated into the standard toxicology program, Gilead Sciences undertook specific studies to better delineate the mechanism underlying the effects on bone. These studies suggest that tenofovir is not directly toxic to bone, instead, data suggest that bone effects are secondary to negative phosphate balance resulting from tenofovir-related reductions in intestinal phosphate absorption and/or renal reabsorption of phosphate. Effects of tenofovir on intestinal absorption and renal reabsorption of phosphate appear to be related to inhibition of NaPi transporter proteins. Secondary effects of tenofovir on bone are dose-, species-, and age-related and are reversible with dose-reduction or discontinuation of treatment.

3.5.4. Genetic and Reproductive Toxicity

The genetic toxicology profile of tenofovir DF is similar to that of marketed nucleoside analogs. Tenofovir DF was negative in the in vitro bacterial mutation (Ames) assay (Salmonella-Eschericia coli/ Mammalian-Microsome Reverse Mutation Assay) but positive in the in vitro mouse lymphoma assay (L5178Y TK+/- Forward Mutation Assay), with and without metabolic activation. Tenofovir DF was negative in the in vivo mouse micronucleus assay at plasma exposure levels of more than 10x the human exposure.

Reproductive toxicity was evaluated in rats and rabbits. Tenofovir DF had no adverse effects on fertility or general reproductive performance in rats at doses up to 600 mg/kg/day. Tenofovir DF had no adverse effects on embryo-fetal development in rats at doses 450 mg/kg/day and in rabbits at doses up to 300 mg/kg/day. In a study of effects on peri- and postnatal development in rats, effects considered due to maternal toxicity (450-600 mg/kg/day) were reduced survival and a slight delay in sexual maturation in the F1 generation. There were no adverse effects on growth, development, behavior, or reproductive parameters at non-maternally toxic doses (150 mg/kg/day).
4. CLINICAL SUMMARY

4.1. Efficacy

4.1.1. Introduction

Results from studies 701 (intravenous tenofovir) and 901 (oral tenofovir DF) provided initial confirmation of the antiviral activity of tenofovir and tenofovir DF, respectively. Following 7 daily doses of tenofovir 1 mg/kg or 3 mg/kg, administered intravenously, patients in study 701 had median decreases of 0.58 and 1.05 \( \log_{10} \) copies/mL in plasma HIV-1 RNA levels, respectively. For patients who received 28 days of repeat daily dosing with tenofovir DF 300 mg once daily in study 901, the median decrease was 1.22 \( \log_{10} \) copies/mL.

In addition to these mixed populations of treatment-naïve and treatment-experienced patients, the effects of tenofovir DF were investigated, in combination with other antiretroviral drugs, in HIV-infected patients whose viral loads were not controlled by their current antiretroviral regimen. Two pivotal placebo-controlled clinical studies (studies 902 and 907) demonstrate the efficacy of tenofovir DF administered in combination with other antiretroviral agents in extensively treatment-experienced HIV-infected patients with a detectable viral load (> 400 copies/mL). Study 902 was a dose-ranging study of three doses of tenofovir DF (75 mg, 150 mg, 300 mg) compared with placebo, and study 907 was a large phase 3 study of tenofovir DF 300 mg compared with placebo. In both studies, an intensification strategy was used in which tenofovir DF was added to existing regimens in a double-blind manner. Significant anti-HIV activity was demonstrated in these antiretroviral-experienced patients despite the fact that 94% of patients in each of the studies had evidence of nucleoside-associated resistance mutations at baseline.

4.1.2. Study 701

The initial clinical evaluation of tenofovir was conducted using an intravenous formulation of the parent compound, tenofovir, administered over one hour. In this placebo-controlled, dose-escalating study, each patient received a total of 8 doses of tenofovir 1 mg/kg, 3 mg/kg or placebo. Dosing occurred on day 1 and on days 8-14; efficacy measures (changes in plasma HIV-1 RNA from baseline and CD4 cell counts) were evaluated periodically through day 42. After 7 days consecutive dosing (days 8-14) patients receiving 1 mg/kg and 3 mg/kg tenofovir had median decreases of 0.58 and 1.05 \( \log_{10} \) copies/mL, respectively. In the 3-mg/kg dose group this decrease was sustained through day 21 without additional dosing.

4.1.3. Study 901

Following completion of the development work on an oral prodrug (tenofovir DF) and with confirmation of the antiviral effect of tenofovir in study 701, study 901 was initiated to confirm the pharmacokinetics, anti-HIV activity and safety of the new oral formulation. The design of this study mimicked that of study 701 with an extension of the daily dosing phase.
to 28 days. This placebo-controlled, dose-escalating study eventually included 4 doses (75 mg, 150 mg, 300 mg, and 600 mg). One further cohort (75 mg tenofovir DF in combination with hydroxyurea) was studied. After completion of the initial 3 cohorts, an open-label safety phase was added for patients who completed the initial study.

Administration of tenofovir DF once daily for a total of 28 days resulted in statistically significant decreases in HIV-1 RNA levels at all dose levels compared with placebo. In an intent-to-treat analysis of all randomized patients, the median decreases in HIV-1 RNA levels at the end of the 28-day dosing period were -0.33 log_{10} copies/mL in the 75 mg group, -0.22 log_{10} copies/mL in the 75 mg + HU group, -0.44 log_{10} copies/mL in the 150 mg group, -0.85 log_{10} copies/mL in the 300 mg, and -0.80 log_{10} copies/mL in the 600 mg group (Figure 4-1).

Figure 4-1. Changes From Baseline in Plasma HIV-1 RNA Levels - Study 901, Blinded Phase

Note: Tenofovir DF 75 mg + HU dose group is not included in graph.

In patients who completed 28 days of dosing, the median decreases in HIV-1 RNA levels were -1.22 and -0.80 log_{10} copies/mL in those who received tenofovir DF 300 mg and 600 mg, respectively. The median decreases in HIV-1 RNA levels were -1.57 log_{10} copies/mL and -1.40 log_{10} copies/mL in patients who had not received previous antiretroviral therapy and -0.97 log_{10} copies/mL and -0.61 log_{10} copies/mL in patients who were antiretroviral-experienced in the tenofovir DF 300 mg and 600 mg groups, respectively,
In extended dosing, in combination with highly active retroviral therapy, decreases in plasma HIV-1 RNA levels from baseline were seen at months 6 and 12.

Except for the tenofovir DF 75 mg + HU arm, all dose groups had increases in CD4 counts; however, none of these changes were statistically significant (Table 4-1). In extended dosing, positive changes in CD4 counts were seen at months 6 and 12.

Pharmacokinetic parameters were evaluated in study 901 and are summarized in section 4.4.2.

**Table 4-1. Changes From Baseline in CD4 Counts (Study 901, Blinded Phase)**

<table>
<thead>
<tr>
<th>CD4 (cells/mm$^3$)</th>
<th>Placebo</th>
<th>Tenofovir DF</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>75 mg</td>
<td>150 mg</td>
<td>300 mg</td>
<td>600 mg</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>N</td>
<td>Mean</td>
<td>Median</td>
<td>Q1 to Q3</td>
<td>Range</td>
</tr>
<tr>
<td>N</td>
<td>11</td>
<td>12</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>347</td>
<td>447</td>
<td>344</td>
<td>432</td>
<td>330</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>373</td>
<td>388</td>
<td>274</td>
<td>375</td>
<td>262</td>
<td></td>
</tr>
<tr>
<td>Q1 to Q3</td>
<td>259 to 444</td>
<td>278 to 435</td>
<td>253 to 466</td>
<td>323 to 564</td>
<td>185 to 289</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>164 to 497</td>
<td>214 to 1035</td>
<td>211 to 557</td>
<td>280 to 655</td>
<td>149 to 743</td>
<td></td>
</tr>
<tr>
<td>Change at Day 8</td>
<td></td>
<td>N</td>
<td>Mean</td>
<td>Median</td>
<td>Q1 to Q3</td>
<td>Range</td>
</tr>
<tr>
<td>N</td>
<td>9</td>
<td>12</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>44</td>
<td>2.1</td>
<td>-24</td>
<td>-17</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>33</td>
<td>9.0</td>
<td>-15</td>
<td>-21</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Q1 to Q3</td>
<td>7 to 40</td>
<td>-49 to 44</td>
<td>-71 to 21</td>
<td>-34 to -11</td>
<td>15 to 64</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>-149 to 395</td>
<td>-82 to 101</td>
<td>-95 to 35</td>
<td>-50 to 42</td>
<td>-81 to 268</td>
<td></td>
</tr>
<tr>
<td>Change to Day 35</td>
<td></td>
<td>N</td>
<td>Mean</td>
<td>Median</td>
<td>Q1 to Q3</td>
<td>Range</td>
</tr>
<tr>
<td>N</td>
<td>9</td>
<td>10</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>74</td>
<td>7</td>
<td>49</td>
<td>7</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>54</td>
<td>42</td>
<td>59</td>
<td>17</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Q1 to Q3</td>
<td>-22 to 94</td>
<td>-65 to 76</td>
<td>15 to 112</td>
<td>-20 to 38</td>
<td>-8 to 137</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>-67 to 302</td>
<td>-176 to 98</td>
<td>-103 to 126</td>
<td>-81 to 74</td>
<td>-70 to 443</td>
<td></td>
</tr>
</tbody>
</table>
4.1.4. Study 902

4.1.4.1. Objectives and Study Design

Study 902 was designed to evaluate the long-term (48-week) safety of three doses used in study 901 and to confirm the efficacy results that had been documented. An intensification design was selected to allow characterization of the antiviral activity associated with tenofovir DF in the setting of a stable background antiretroviral regimen. Patients had to be on stable antiretroviral therapy, consisting of no more than four active agents, for at least 8 weeks prior to enrollment.

Between September 1998 and March 1999, 189 patients were randomized in a 2:2:2:1 ratio to add either tenofovir DF at one of three doses (75 mg, 150 mg, or 300 mg once daily) or placebo to their existing regimen in a double-blinded manner. At 24 weeks post-randomization, patients who had received placebo were crossed over to tenofovir DF 300 mg once daily in a blinded fashion for the remainder of the initial 48-week study period (Figure 4-2). Following 48 weeks, patients were offered open-label tenofovir DF 300 mg with continued follow-up. Recently, all patients remaining on this study were rolled over to study 910 for continued long-term follow-up.

Figure 4-2. Treatment Schedule in Study 902

<table>
<thead>
<tr>
<th></th>
<th>24 wks</th>
<th>48 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable ART ≥ 8 weeks randomized</td>
<td>300 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>2:2:2:1</td>
<td>75 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>Placebo</td>
<td>300 mg</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

n = 186

4.1.4.2. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for study 902 were designed to select a study population that was representative of treatment experienced HIV-infected patients with a detectable viral load. The principal selection criteria was based on plasma HIV-1 RNA levels:

- ≥ 400 copies/mL and ≤ 100,000 copies/mL in patients currently receiving stable anti-
retroviral therapy. Other key inclusion criteria were related to the requirements for adequate renal, hepatic and hematologic function. Patients were stratified by site according to HIV-1 RNA level (≤ 5000 copies/mL, > 5,000 copies/mL), CD4 count (≤ 200 cells/mL, > 200 cells/mL), and number of antiretroviral drugs prior to study entry (≤ 4, > 4).

4.1.4.3. Efficacy Endpoints

The primary and key secondary efficacy endpoints are summarized below.

Primary Efficacy Endpoint

- The time-weighted average change from baseline in log_{10} copies/mL plasma HIV-1 RNA levels up to week 4 (DAVG4) and to week 24 (DAVG24).

Key Secondary Efficacy Endpoints

- The time-weighted average change from baseline in log_{10} copies/mL HIV-1 RNA levels up to week 48 post-randomization (DAVG48).
- The proportion of patients with plasma HIV-1 RNA levels at or below quantification limits (≤ 400 copies/mL and HIV-1 RNA ≤ 50 copies/mL) during the study period.
- Mean change from baseline and time-weighted average change (DAVG) from baseline in CD4 count.

Plasma HIV-1 RNA is widely accepted as a highly predictive surrogate marker of HIV-1 disease progression in HIV-1 infected patients.\textsuperscript{71} The DAVG endpoint allows measurements at varying timepoints to contribute to the overall measurement of efficacy and is less sensitive to missing data than an endpoint based on a single data point. The assessment of the CD4 subset of T-cell immunophenotypes provides a well-validated marker of immune competence in HIV disease. The utility of both the virologic and immunologic markers have been validated in numerous natural history and clinical studies of antiretroviral agents in HIV-1 infected patients.

4.1.4.4. Patient Disposition

Of 189 HIV-1 infected patients enrolled in study 902, 3 patients did not receive study medication (one in the tenofovir DF 75 mg group and two in the tenofovir DF 300 mg group). Across the four treatment groups, 26 patients (14%) discontinued study medication before week 24. For the tenofovir DF treatment groups, the discontinuation rates ranged from 9% to 16% compared with 25% for the placebo group (Table 4-2).

Of the 28 patients who were originally randomized to placebo, 21 crossed over to active treatment with tenofovir DF 300 mg once daily upon completion of week 24. The remaining seven placebo patients (25%) had discontinued by week 24. After week 24, a further 22 patients (11%) discontinued from the study prior to the week 48 visit (9 in the tenofovir DF 75 mg group, 4 in the tenofovir DF 150 mg group, 7 in the tenofovir DF
300 mg group, and 2 in the placebo/tenofovir 300 mg crossover group). Further information regarding the reasons for study discontinuation is detailed in section 4.3.2.

Table 4-2. Disposition of Patients Up to 24 Weeks: Study 902

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Total</th>
<th>Placebo</th>
<th>Tenofovir DF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>75 mg</td>
</tr>
<tr>
<td>Number of Patients Randomized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>189 (100%)</td>
<td>28 (100%)</td>
<td>54 (100%)</td>
</tr>
<tr>
<td>Received No Study Medication</td>
<td>3 (2%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Received ≥ 1 Dose of Study Medication &amp; Discontinued Before Week 24</td>
<td>26 (14%)</td>
<td>7 (25%)</td>
<td>5 (9%)</td>
</tr>
</tbody>
</table>

4.1.4.5. Demographic and Other Baseline Characteristics

The demographic characteristics of patients who participated in study 902 were representative of the HIV-1 infected patient population (Table 4-3). The majority of patients were male and Caucasian and the mean age was 42 years; treatment groups were well matched with respect to these characteristics.
Table 4-3. Demographic and Baseline Disease Characteristics (Study 902, ITT Population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study 902 (N = 186)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>41.9</td>
</tr>
<tr>
<td>Median</td>
<td>41.1</td>
</tr>
<tr>
<td>Range</td>
<td>27.3 to 62.3</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>171 (92%)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>15 (8%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>138 (74%)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>24 (13%)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>21 (11%)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>CD4 count (cells/mm^3)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>374 (235)</td>
</tr>
<tr>
<td>Median</td>
<td>331</td>
</tr>
<tr>
<td>Range</td>
<td>9 to 1240</td>
</tr>
<tr>
<td>HIV-1 RNA</td>
<td></td>
</tr>
<tr>
<td>Mean (copies/mL)</td>
<td>16,583</td>
</tr>
<tr>
<td>Mean (SD) (log_10 copies/mL)</td>
<td>3.66 (0.68)</td>
</tr>
<tr>
<td>Range (log_10 copies/mL)</td>
<td>1.72 to 5.76</td>
</tr>
<tr>
<td>Prior ART experience</td>
<td></td>
</tr>
<tr>
<td>Mean duration (years)</td>
<td>4.6</td>
</tr>
<tr>
<td>HIV-1 Resistance Mutations*</td>
<td></td>
</tr>
<tr>
<td>Substudy, n</td>
<td>184</td>
</tr>
<tr>
<td>NRTI, n (%)</td>
<td>173 (94%)</td>
</tr>
<tr>
<td>PI, n (%)</td>
<td>105 (57%)</td>
</tr>
<tr>
<td>NNRTI, n (%)</td>
<td>58 (32%)</td>
</tr>
</tbody>
</table>

* NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor.

The mean viral load of the study populations was 3.7 log_{10} copies/mL plasma HIV-1 RNA and was consistent across the treatment groups. There was some variation across the treatment groups ranging from 298 cells/mm^3 for the placebo group to 410 cells/mm^3 for the tenofovir DF 150 mg group.

All patients had substantial prior exposure to antiretroviral therapy and most patients had evidence of resistance mutations. Baseline genotypic analysis revealed that 94% of patients...
in both studies had plasma HIV-1 expressing one or more primary nucleoside-associated resistance mutations in RT (Resistance Collaborative Group definition). HIV-1 expressing primary protease inhibitor-associated resistance mutations were also frequent (57%) as were primary NNRTI-associated resistance mutations (32%). The incidence of mutations was similar across the treatment groups. Baseline antiretroviral therapy regimens ranged from nucleoside monotherapy to dual NRTI therapy and HAART regimens.

4.1.4.6. Efficacy Results

4.1.4.6.1. Time Weighted Average Changes from Baseline (DAVG) in Log_{10} Copies/mL HIV-1 RNA Levels

Statistically significant changes from baseline in plasma HIV-1 RNA levels (log_{10} copies/mL) were demonstrated for each of the tenofovir treatment groups when compared with placebo at week 4 and week 24 (Figure 4-3 and Table 4-4). The greatest effect was seen with the tenofovir DF 300 mg group with mean changes of -0.62 log_{10} copies/mL at week 4 and -0.58 log_{10} copies/mL at week 24 compared with a +0.2 log_{10} copies/mL changes in the placebo group at both timepoints.

Figure 4-3. Mean Change from Baseline in HIV-1 RNA (Study 902)
### Table 4-4. Time-Weighted Average Changes from Baseline (DAVG) in Log_{10} Copies/mL Plasma HIV-1 RNA Levels Through Weeks 4, 24 and 48: Study 902 (ITT Population)

<table>
<thead>
<tr>
<th>DAVG_{x/x} Group</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Q1, Q3</th>
<th>P-Value</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAVG_{4}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>+0.02 (0.39)</td>
<td>-0.04</td>
<td>-0.17, +0.20</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>75 mg</td>
<td>-0.22 (0.35)</td>
<td>-0.14</td>
<td>-0.46, -0.03</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>150 mg</td>
<td>-0.44 (0.42)</td>
<td>-0.36</td>
<td>-0.72, -0.19</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>300 mg</td>
<td>-0.62 (0.49)</td>
<td>-0.56</td>
<td>-1.02, -0.25</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>DAVG_{24}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>+0.02 (0.69)</td>
<td>+0.04</td>
<td>-0.20, +0.42</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>75 mg</td>
<td>-0.26 (0.51)</td>
<td>-0.16</td>
<td>-0.43, +0.06</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>150 mg</td>
<td>-0.34 (0.59)</td>
<td>-0.23</td>
<td>-0.74, -0.06</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>300 mg</td>
<td>-0.58 (0.63)</td>
<td>-0.54</td>
<td>-0.96, -0.12</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>DAVG_{48}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 mg</td>
<td>-0.33 (0.59)</td>
<td>-0.29</td>
<td>-0.59, +0.06</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>150 mg</td>
<td>-0.34 (0.59)</td>
<td>-0.29</td>
<td>-0.77, -0.00</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>300 mg</td>
<td>-0.62 (0.63)</td>
<td>-0.61</td>
<td>-1.04, -0.25</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Note: Placebo comparison not possible at week 48 due to crossover of placebo patients to tenofovir DF 300 mg.

a Quartile 1 (25%), Quartile 3 (75%).

b p-value versus placebo, Wilcoxon rank sum test, not stratified.

Furthermore, while comparison with the placebo group at the 48-week timepoint is not possible due to the crossover to tenofovir DF 300 mg at week 24, it appears that the antiviral response to tenofovir DF in the three active treatment groups was sustained through 48 weeks (Table 4-4). Again, the greatest effect was seen with the tenofovir DF 300 mg group with a mean change of -0.62 log_{10} copies/mL.

Examination of the mean log_{10} copies/mL changes in plasma HIV-1 RNA at all time points (i.e., weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 48), demonstrated that the tenofovir DF 150 mg and 300 mg groups, had diverged from the placebo group after one week of active treatment. At week 4, all three active treatment groups were significantly different from the placebo group (p = 0.008 for 75 mg; p < 0.001 for 150 and 300 mg). At week 24, the mean change for the tenofovir DF 300 mg group was -0.58 log_{10} copies/mL compared with a +0.02 log_{10} copies/mL mean change in the placebo group. At week 48, the mean reduction was -0.62 log_{10} copies/mL for the tenofovir DF 300 mg group.
4.1.4.6.2. Percentage of Patients With Plasma HIV-1 RNA at or Below Lower Limit of Quantification

Two plasma HIV-1 RNA assays were used in the study, the Amplicor HIV-1 Monitor™ Test with a lower limit of quantification of 400 copies/mL and the Ultrasensitive HIV-1 Monitor™ Test with a lower limit of quantification of 50 copies/mL. Measurements of plasma HIV-1 RNA denoted as < 50 or < 400 copies/mL were considered to have achieved values below the lower limit of quantification of the respective assay. Although the study was not powered to detect significant differences in the proportion of patients with HIV-1 RNA at or below limits of quantification, these data provide further evidence of the anti-HIV-1 activity of tenofovir DF.

For the ITT population, patients without plasma HIV-1 RNA values were included as treatment failures (plasma HIV-1 RNA levels above 400 or 50 copies/mL). Using this analysis strategy, the percentages at week 24 were not significantly different between the tenofovir groups and the placebo group for both plasma HIV-1 RNA ≤ 400 copies/mL and for plasma HIV-1 RNA ≤ 50 copies/mL. The proportion of patients with plasma HIV-1 RNA ≤ 400 copies/mL was 26% in the tenofovir DF 300 mg group and 21% in the placebo group; for the proportion of patients with plasma HIV-1 RNA ≤ 50 copies/mL, 13% in the tenofovir DF 300 mg group and 11% in the placebo group achieved this endpoint (Table 4-5).

An additional analysis was performed on the as-treated (AT) population which differs from the ITT population by excluding all data after permanent discontinuation of assigned study medication or addition of other antiretroviral medication. The AT analysis would, therefore, exclude data collected from patients who changed background therapy to achieve maximal suppression of viral load with the data exclusion beginning after the timepoint that patients changed background therapy.

When the AT population was analyzed for the proportion of patients with plasma HIV-1 RNA ≤ 400 copies/mL at week 24, 4% of patients in the placebo group achieved this value, compared to 19% of patients in the tenofovir DF 300 mg group. Furthermore, when the AT population was analyzed for the proportion of patients with plasma HIV-1 RNA ≤ 50 copies/mL at week 24, 11% in the tenofovir DF 300 mg group achieved this value, whereas no patients in the placebo group achieved this endpoint (Table 4-5). Although the study was not powered to detect significant differences in the proportion of patients with HIV-1 RNA ≤ 400 or ≤ 50 copies/mL, these data further indicate the anti-HIV-1 activity of tenofovir DF.
Table 4-5. Proportion of Patients at Week 24 With Plasma HIV-1 RNA ≤ 400 copies/mL and ≤ 50 copies/mL: Study 902 (ITT and AT Populations)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Tenofovir DF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>75 mg</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>≤ 400 Copies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>6/28 (21%)</td>
<td>12/53 (23%)</td>
</tr>
<tr>
<td>AT</td>
<td>1/28 (4%)</td>
<td>5/53 (9%)</td>
</tr>
<tr>
<td>≤ 50 Copies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>3/28 (11%)</td>
<td>7/53 (13%)</td>
</tr>
<tr>
<td>AT</td>
<td>0/28 (0%)</td>
<td>2/53 (4%)</td>
</tr>
</tbody>
</table>

4.1.4.6.3. Effect on CD4 Cell Counts

Changes in CD4 counts did not differ significantly between the active groups and the placebo group at any assessment time point during treatment. Mean changes in CD4 cell counts at the 24 week timepoint were difficult to interpret (+20 cells/mm³, +18 cells/mm³, 0 cells/mm³, and -14 cells/mm³ in the placebo, 75 mg, 150 mg, and 300 mg groups, respectively). However, the mean changes in CD4 percentage were identical and positive in the three tenofovir DF groups (+0.4%); in contrast, the placebo group exhibited a decrease from baseline of -1.1% at this time point.

All three active treatment groups had positive changes in CD4 cell count at week 48. Mean changes were +10 cells/mm³, +20 cells/mm³ and +11 cells/mm³ in the 75 mg, 150 mg, and 300 mg groups, respectively. The mean changes in CD4% in the tenofovir DF groups remained positive at week 48 and had further increased in the two higher-dose groups (+0.3%, +1.2%, and +0.8% in the 75 mg, 150 mg, and 300 mg dose groups, respectively).

4.1.4.7. Efficacy in Long-Term Use (> 48 Weeks)

In study 902 patients were given the option to continue into an open-label protocol and to receive tenofovir DF 300 mg once daily until either the drug is licensed or the Sponsor discontinues the study. At the time of the NDA submission, interim long-term data were available for the 902 extension phase. The primary objective of the 902 extension phase was to define the long-term safety profile of tenofovir DF when dosed at 300 mg once daily. In addition, plasma HIV-1 RNA and CD4 cells counts were monitored to measure virologic efficacy in extended treatment and are briefly reviewed in this section. The total number of patients who continued from the double-blind phase of study 902 into the open-label phase was 135.
Results for the extension phase demonstrate durable antiviral activity with mean decreases from baseline in plasma HIV-1 RNA observed at all visits and in all treatment groups. For the treatment groups that had received tenofovir DF throughout the double-blind phase, mean decreases from baseline in plasma HIV-1 RNA levels ranged from $\geq 0.6 - 1.2 \log_{10}$ copies/mL (Table 4-6) during the extension phase.

Table 4-6. Changes from Baseline in Plasma HIV-1 RNA ($\log_{10}$ Copies/mL) at Weeks 72 and 96 (ITT Population): Study 902 Extension Phase

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose group (0-48 Weeks/Extension)</th>
<th>(24-48 Weeks /Extension)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75/300 (N = 37)</td>
<td>150/300 (N = 37)</td>
</tr>
<tr>
<td>Week 72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>-0.66 (1.28)</td>
<td>-0.64 (0.75)</td>
</tr>
<tr>
<td>Median</td>
<td>-0.69</td>
<td>0.66</td>
</tr>
<tr>
<td>Week 96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>-1.17 (1.27)</td>
<td>-0.66 (1.24)</td>
</tr>
<tr>
<td>Median</td>
<td>-1.48</td>
<td>-0.68</td>
</tr>
</tbody>
</table>

Note: baseline plasma HIV-1 RNA levels for the 75/300 mg, 150/300 mg and 300/300 mg groups is defined as the average of the pre-treatment values taken after screening. Baseline for the placebo crossover/300 mg group is defined as the last assessment occurring on or before active study medication was dispensed.

All tenofovir DF treatment groups demonstrated increases from baseline in mean CD4 cell counts (Table 4-7). At week 96, the mean increase in CD4 cell count ranged from 31.4 cells/mm$^3$ (300/300 mg group) to 80.9 cells/mm$^3$ (placebo crossover/300 mg group).
Table 4-7. Mean Change from Baseline In CD4 Cell Count at Weeks 72 and 96 (ITT Population): Study 902 Extension Phase

<table>
<thead>
<tr>
<th>Dose Group (0-48 Weeks/Extension)</th>
<th>(24-48 Weeks/Extension)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tenofovir DF</td>
</tr>
<tr>
<td>75/300 (N = 37)</td>
<td>150/300 (N = 37)</td>
</tr>
<tr>
<td>Week 72</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>35</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>36.2±118.1</td>
</tr>
<tr>
<td>Week 96</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>19</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>67.1±125.4</td>
</tr>
</tbody>
</table>

Note: baseline plasma HIV-1 RNA levels for the 75/300 mg, 150/300 mg and 300/300 mg groups is defined as the average of the pre-treatment values taken after screening. Baseline for the placebo crossover/300 mg group is defined as the last assessment occurring on or before active study medication was dispensed.

Tenofovir DF 300 mg once daily demonstrated improved virologic suppression and immunologic benefit during long-term treatment (up to 96 weeks) when used in combination antiretroviral therapy in treatment-experienced HIV-infected patients.

4.1.5. Study 907

4.1.5.1. Objectives and Study Design

The primary objective of study 907 was to evaluate the safety and efficacy of tenofovir DF 300 mg in a large population. An intensification design was again selected to enable characterization of the antiviral activity of tenofovir DF.

In this study, 552 patients were randomized in a 2:1 ratio to add tenofovir DF 300 mg once daily or placebo to their existing regimen in a blinded manner. Dose selection in this study was based on the greater antiviral effect of 300 mg tenofovir DF observed in study 901 and the results of study 902, which demonstrated a lack of dose-related toxicity.

Patients and physicians were discouraged from altering background antiretroviral regimens until at least 24 weeks post-randomization. Thereafter, changes in background antiretroviral therapy were permitted while all patients continued open-label tenofovir DF 300 mg. On completion of 48 weeks of study, patients were offered continued open-label tenofovir DF with follow-up in study 910.
4.1.5.2. Inclusion and Exclusion Criteria

As in study 902, the inclusion and exclusion criteria for study 907 were designed to select a study population that was representative of treatment experienced HIV-infected patients with a detectable viral load. The principal selection criteria was based on plasma HIV-1 RNA levels ≥ 400 copies/mL to ≤ 10,000 copies/mL (using the Roche Standard Amplicor™ HIV-1 Monitor Test) in patients currently receiving stable antiretroviral therapy. Other key inclusion criteria were related to the requirements for adequate renal, hepatic and hematologic function. Patients were stratified by site according to HIV-1 RNA level (≤ 5000 copies/mL, > 5000 copies/mL), CD4 count (≤ 200 cells/mL, > 200 cells/mL), and number of antiretroviral drugs prior to study entry (≤ 4, > 4).

4.1.5.3. Efficacy Endpoints

The primary and key secondary efficacy endpoints based on these outcome are summarized below.

**Primary Efficacy Endpoint**
- The time-weighted average change from baseline in \( \log_{10} \) copies/mL plasma HIV-1 RNA levels up to week 24 (DAVG24).

**Key Secondary Efficacy Endpoints**
- The proportion of patients with plasma HIV-1 RNA levels at or below quantification limits (≤ 400 copies/mL and HIV-1 RNA ≤ 50 copies/mL) during the study period.
• Mean change from baseline and time-weighted average change (DAVG) from baseline in CD4 count.

4.1.5.4. Patient Disposition

Of the 552 HIV-1 infected patients randomized in study 907, two patients discontinued the study prior to receiving any study medication and were excluded from the analysis. A total of 34 patients (6% of patients in both the tenofovir DF 300 mg and placebo treatment groups) discontinued study medication before week 24 (Table 4-8). Further information regarding reasons for study discontinuation is detailed in section 4.3.2.

Table 4-8. Disposition of Patients Up to 24 Weeks: Study 907

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Total</th>
<th>Placebo</th>
<th>Tenofovir DF 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients Randomized</td>
<td>552 (100%)</td>
<td>184 (100%)</td>
<td>368 (100%)</td>
</tr>
<tr>
<td>Received No Study Medication</td>
<td>2 (&lt;1%)</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Received ≥ 1 Dose of Study Medication &amp; Discontinued Before Week 24</td>
<td>34 (6%)</td>
<td>11 (6%)</td>
<td>23 (6%)</td>
</tr>
</tbody>
</table>

4.1.5.5. Demographics and Other Baseline Characteristics

The demographic characteristics of patients who participated in study 907 were representative of the HIV-1 infected patient population (Table 4-9). The majority of patients were male and Caucasian and the mean age was 42 years; treatment groups were well matched with respect to these characteristics.
### Table 4-9. Demographic and Baseline Disease Characteristics (Study 907, ITT Population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study 907 (N = 550)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>41.6</td>
</tr>
<tr>
<td>Median</td>
<td>40.0</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>469 (85%)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>81 (15%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>379 (69%)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>92 (17%)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>68 (12%)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td><strong>CD4 count (cells/mm³)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>427 (214)</td>
</tr>
<tr>
<td>Median</td>
<td>386</td>
</tr>
<tr>
<td>Range</td>
<td>23 to 1385</td>
</tr>
<tr>
<td><strong>HIV-1 RNA</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (copies/mL)</td>
<td>4440</td>
</tr>
<tr>
<td>Mean (SD) (log₁₀ copies/mL)</td>
<td>3.36 (0.51)</td>
</tr>
<tr>
<td>Range (log₁₀ copies/mL)</td>
<td>1.70 to 4.88</td>
</tr>
<tr>
<td><strong>Prior ART experience</strong></td>
<td></td>
</tr>
<tr>
<td>Mean duration (years)</td>
<td>5.4</td>
</tr>
<tr>
<td><strong>HIV-1 Resistance Mutations</strong></td>
<td></td>
</tr>
<tr>
<td>Substudy, n</td>
<td>253</td>
</tr>
<tr>
<td>NRTI, n (%)</td>
<td>238 (94%)</td>
</tr>
<tr>
<td>PI, n (%)</td>
<td>148 (58%)</td>
</tr>
<tr>
<td>NNRTI, n (%)</td>
<td>121 (48%)</td>
</tr>
</tbody>
</table>

* NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor.

The mean viral load of the study populations $3.4 \log_{10}$ copies/mL plasma HIV-1 RNA and was consistent across the treatment groups; the two treatment groups were similar with respect to the mean CD4 count at baseline.

All patients had substantial prior exposure to antiretroviral therapy and most patients had evidence of resistance mutations. Baseline genotypic analysis revealed that 94% of patients had plasma HIV-1 expressing one or more primary nucleoside-associated resistance
mutations in RT (Resistance Collaborative Group definition).\textsuperscript{72} HIV-1 expressing primary protease inhibitor-associated resistance mutations were also frequent (58%) as were primary NNRTI-associated resistance mutations (48%). The incidence of mutations was similar across the treatment groups. Baseline antiretroviral therapy regimens ranged from nucleoside monotherapy to dual NRTI therapy and HAART regimens.

4.1.5.6. Efficacy Results

4.1.5.6.1. Time Weighted Average Changes from Baseline (DAVG) in Log_{10} copies/mL HIV-1 RNA Levels

The results of the primary efficacy endpoint demonstrate the significant antiviral activity of tenofovir DF. The time-weighted average change from baseline through week 24 (DAVG\textsubscript{24}) for Log_{10} copies/mL plasma HIV-1 RNA was significantly greater for the tenofovir DF 300 mg group (-0.61 Log_{10} copies/mL) compared to the placebo group (-0.03 Log_{10} copies/mL) (Figure 4-5 and Table 4-10). Two sensitivity analyses (one with the last observation carried forward, one with the baseline value carried forward) supported the results of the primary analysis (p < 0.001 for tenofovir DF vs. placebo in both analyses).
Figure 4-5. Mean and 95% CI in Change From Baseline in $\log_{10}$ Plasma HIV-1 RNA Levels Over Time, Intent-to-Treat Population (Study 907)

Note: The lower limit of quantification, 50, is substituted for values of HIV-1 RNA below 50.
Table 4-10.  

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tenofovir 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>-0.03 (0.36)</td>
<td>-0.61 (0.61)</td>
</tr>
<tr>
<td>Median</td>
<td>-0.02</td>
<td>-0.56</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>-0.22, +0.19</td>
<td>-1.07, -0.15</td>
</tr>
<tr>
<td>P-Value</td>
<td>-</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* Quartile 1 (25%), Quartile 3 (75%).  

b p-value versus placebo, Wilcoxon rank sum test, not stratified (primary analysis); the p-value was the same using stratified Wilcoxon rank sum test.

The time-weighted average changes in log_{10} copies/mL plasma HIV-1 RNA at all time points assessed (i.e. weeks 2, 4, 8, 12, 16, 20, 24), were all significantly superior for the tenofovir DF 300 mg group compared with the placebo group (p<0.001).

4.1.5.6.2.  Percentage of Patients With Plasma HIV-1 RNA at or Below Lower Limit of Quantification

Further evidence of the anti HIV-1 activity of tenofovir DF is provided by the evaluation of the proportion of patients who achieved HIV-1 RNA levels at or below limits of quantification over the course of the 24-week treatment period.

In the ITT population, using the conservative strategy of patients without plasma HIV-1 RNA values as having plasma HIV-1 RNA levels above 400 or 50 copies/mL, significant treatment effects were observed with tenofovir DF treatment compared with placebo (Table 4-11). The percentage of patients with plasma HIV-1 RNA ≤ 400 copies/mL at week 24 was 42% (155/368) in the tenofovir DF 300 mg group compared to 13% (23/182) in patients receiving placebo. The percentage of patients with plasma HIV-1 RNA ≤ 50 copies/mL at week 24 was 21% (76/368) in the tenofovir DF 300 mg group compared to 1% (2/182) in patients receiving placebo (Table 4-11). The results of this analysis using the AT population, which included all patients who received at least one dose of study medication but excluded all data after discontinuation of assigned study medication and/or addition of other antiretroviral therapy, were similar to the results using the ITT population.
Table 4-11. Proportion of Patients at Week 24 with Plasma HIV-1 RNA ≤ 400 copies/mL and ≤ 50 copies/mL: Study 907 (ITT Population)

<table>
<thead>
<tr>
<th>HIV-1 RNA</th>
<th>Placebo</th>
<th>Tenofovir DF 300 mg</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 400 copies/mL</td>
<td>23/172 (13%)</td>
<td>155/346 (45%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>≤ 50 copies/mL</td>
<td>2/155 (1%)</td>
<td>7/325 (22%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

* CMH General Association Test

4.1.5.6.3. Effect on CD4 Cell Counts

The efficacy of tenofovir DF in this population of HIV-1 infected patients was also evident from the immunologic effect on the level of CD4 cell counts. Treatment with tenofovir DF resulted in mean time-weighted average change from baseline in CD4 count of 12 cells/mm³ occurring at week 24. The change at week 24 for CD4 count represented a significant difference between tenofovir DF 300 mg versus placebo (p-value = 0.0008). A statistically significant difference favoring tenofovir DF was seen at every on-treatment assessment time point for the time-weighted average change from baseline in CD4 cell count (Table 4-12).

The mean and 95% CI in change from baseline in CD4 cell counts (cells/mm³) over time is presented in Figure 4-6.

Table 4-12. Time-Weighted Average Change from Baseline in CD4 Cell Counts: Study 907 (ITT Population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Placebo (N = 182)</th>
<th>Tenofovir DF (N = 368)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Cell Count</td>
<td>447.1 (216.8)</td>
<td>417.4 (211.7)</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean (± SD) Time-Weighted Average Change from Baseline (cells/mm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>-14.1 (90.9)</td>
<td>6.4 (97.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Week 8</td>
<td>-13.2 (79.5)</td>
<td>6.6 (84.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Week 12</td>
<td>-12.0 (82.7)</td>
<td>9.2 (81.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Week 16</td>
<td>-12.2 (82.8)</td>
<td>10.7 (78.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Week 20</td>
<td>-11.0 (89.7)</td>
<td>12.2 (79.0)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Week 24</td>
<td>-10.6 (88.4)</td>
<td>12.6 (78.4)</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

* Wilcoxon rank sum test
4.1.5.6.4. **Subgroup Analyses**

The anti-HIV-1 activity of tenofovir DF in study 907 was confirmed across a range of subgroups based on demographic characteristics (age, gender and race) and baseline disease status (HIV-1 RNA level, CD4 cell count). All subgroup analyses were evaluated using the time-weighted average change from baseline through week 24 (DAVG24) in plasma HIV-1 RNA (log_{10} copies/mL) and p-values were based on the Wilcoxon rank sum test.

The results of these analyses demonstrate a consistent treatment effect across all subgroups evaluated, that is, in all subgroups there was a significant difference in DAVG_{24} in plasma HIV-1 RNA (log_{10} copies/mL) for patients receiving tenofovir DF compared to patients receiving placebo (Table 4-13). Of the population characteristics investigated, none was predictive of a different antiviral effect than that observed for the group as a whole.
## Table 4-13.

Time-Weighted Average Changes from Baseline up to Week 24 (DAVG24) in log10 Copies/mL Plasma HIV-1 RNA Levels by Demographic and Disease Characteristic Subgroup: Study 907 (ITT Population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subgroup</th>
<th>DAVG24</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>TDF 300 mg</td>
<td>P-Value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Age</td>
<td>≤40 years</td>
<td>n=93</td>
<td>-0.05 (±0.38)</td>
<td>-0.128 to 1.01</td>
</tr>
<tr>
<td></td>
<td>&gt;40 years</td>
<td>n=89</td>
<td>-0.01 (±0.33)</td>
<td>-1.35 to 0.85</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>n=160</td>
<td>-0.02 (±0.36)</td>
<td>-1.35 to 1.01</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>n=22</td>
<td>-0.08 (±0.38)</td>
<td>-1.28 to 0.56</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian</td>
<td>n=118</td>
<td>-0.02 (±0.37)</td>
<td>-1.28 to 1.01</td>
</tr>
<tr>
<td></td>
<td>Non-Caucasian</td>
<td>n=64</td>
<td>-0.05 (±0.34)</td>
<td>-1.35 to 0.85</td>
</tr>
<tr>
<td>HIV-1 RNA</td>
<td>&lt; 5000 copies/mL</td>
<td>n=139</td>
<td>0.03 (±0.33)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>≥ 5000 copies/mL</td>
<td>n=43</td>
<td>-0.22 (±0.38)</td>
<td>-1.35 to 0.40</td>
</tr>
<tr>
<td>CD4 Count</td>
<td>&lt; 200 cells/mm³</td>
<td>n=21</td>
<td>0.05 (±0.37)</td>
<td>-0.85 to 0.84</td>
</tr>
<tr>
<td></td>
<td>≥ 200 cells/mm³</td>
<td>n=161</td>
<td>-0.04 (±0.35)</td>
<td>-1.35 to 1.01</td>
</tr>
</tbody>
</table>
4.1.6. Efficacy Conclusions

Two placebo-controlled clinical studies of tenofovir DF (studies 902 and 907) demonstrate that tenofovir DF 300 mg once daily, when used in combination with other antiretroviral drugs, is effective for the treatment of HIV-1 infected patients who have failed or are intolerant to nucleoside analog therapy, or are not controlled by their current antiretroviral regimen. Efficacy was demonstrated based on significant changes in established and validated surrogate markers for HIV-1 disease (plasma HIV-1 RNA) and immune competence (CD4 cell count), in patients who received tenofovir DF 300 mg daily in combination with standard antiretroviral therapy at 24 weeks (studies 902 and 907) and for up to 48 weeks (study 902 only).

The principal clinical efficacy findings in study 907, the primary phase 3 study, at week 24 are as follows:

- Treatment with tenofovir DF 300 demonstrated a significant reduction in the time-weighted average change from baseline (DAVG24) in log₁₀ copies/mL plasma HIV-1 RNA level (-0.61 log₁₀ copies/mL) compared with placebo (-0.03 log₁₀ copies/mL).
- A significantly higher proportion of tenofovir DF patients achieved plasma HIV-1 RNA levels at or below the limit of quantification (≤ 400 copies/mL 42%; ≤ 50 copies/mL 21%) compared with placebo treatment (≤ 400 copies/mL 13%; ≤ 50 copies/mL 1%).
- There was a significant increase in the time-weighted average change from baseline (DAVG24) in the CD4 cell count.
- Consistently significant reductions from baseline in log₁₀ copies/mL plasma HIV-1 RNA levels were observed in all subgroups based on demographic and disease characteristics.
- Tenofovir DF 300 mg daily demonstrated significant anti-HIV-1 activity in patients with HIV-1 expressing resistance mutations associated with nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

The principal efficacy findings in study 902, the phase 2 dose-finding study, are as follows:

- Statistically significant reductions in the time-weighted average change from baseline in log₁₀ copies/mL plasma HIV-1 RNA levels were demonstrated for each of the tenofovir DF treatment groups when compared with placebo at week 4 and week 24.
- The greatest antiviral effect was seen with tenofovir DF 300 mg with mean changes of -0.62 and -0.58 log₁₀ copies/mL at week 4 and 24, respectively, providing further support for the selection of this dose for the treatment of HIV-infected patients.
- The antiviral response was sustained through 48 weeks as demonstrated by the mean change from baseline of -0.62 log₁₀ copies/mL at week 48 for the tenofovir DF 300 mg treatment group.
• Significant anti-HIV-1 activity was demonstrated in patients with HIV-1 expressing resistance mutations associated with nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

The effects of tenofovir DF 300 mg daily in study 907 with respect to plasma HIV-1 RNA and CD4 cell count when added to intensify therapies due to incomplete suppression of virus are generally consistent with results reported from a similar placebo-controlled phase 3 study of abacavir 300 mg twice daily when added to failing background therapy. The abacavir study population was similar with baseline plasma HIV-1 RNA levels between 400 and 50,000 copies/mL and CD4 counts of at least 100 cells/mm³. However, only 6% of the patients in this trial had 18 months or more of prior antiretroviral therapy, making this population notably less antiretroviral-experienced than the populations in study 907.

Median plasma HIV-1 RNA levels at baseline were 3.68 log₁₀ copies/mL and 3.53 log₁₀ copies/mL for the abacavir and placebo groups, respectively. In study 907, median baseline plasma HIV-1 RNA levels were 3.37 log₁₀ copies/mL for both tenofovir DF-treated patients and for those receiving placebo. At week 16, the addition of abacavir to stable background therapy resulted in a median change in plasma HIV-1 RNA from baseline of -0.44 log₁₀ copies/mL, and the proportion of patients with plasma HIV-1 RNA ≤ 400 copies/mL was 39%. By comparison, in study 907 at week 16, the median change in plasma HIV-1 RNA from baseline was -0.57 log₁₀ copies/mL, and the proportion of patients with HIV-1 RNA ≤ 400 copies/mL was 43% in patients treated with tenofovir DF.

At week 16, abacavir patients had a change in median CD4 count from baseline of 30 cells/mm³ (range, -285 to 485 cells/mm³), which did not differ significantly from patients randomized to placebo (p = 0.093). In study 907, the median change from baseline in CD4 count observed at week 16 with tenofovir DF 300 mg per day was +10 cells/mm³ (range, -411 to 725). The results of both studies suggest that in treatment-experienced patients, the addition of a single antiretroviral agent to stable background therapy can result in significant reductions in plasma HIV-1 RNA with only small changes occurring in CD4 counts.

In conclusion, tenofovir DF 300 mg once daily demonstrates statistically significant antiviral activity in highly treatment-experienced HIV-infected patients with corresponding baseline genotypic evidence of nucleoside-resistant virus.

4.2. Virology

Results of in vitro resistance studies are summarized as an introduction to this section. HIV virology studies have been performed in conjunction with clinical trials of tenofovir and tenofovir DF for the treatment of HIV-infected patients. The objectives of these virology studies were to:

• Determine whether RT resistance mutations develop during tenofovir DF therapy.
• Determine whether any RT mutations that develop correlate with reduced susceptibility of the mutant HIV to tenofovir in vitro or with increasing HIV viral load in vivo.

• Determine whether the baseline HIV RT genotype in antiretroviral experienced patients affects treatment response to tenofovir DF.

Results from clinical resistance analyses demonstrate the significant antiviral efficacy of tenofovir through 48 weeks in patients with extensive nucleoside resistance in their HIV at baseline, and a low incidence of genotypic or phenotypic resistance to tenofovir arising during 24-48 weeks of tenofovir DF therapy.

4.2.1. Summary of Nonclinical Resistance

Results of in vitro resistance evaluations show:

• Tenofovir remains active (within 2-fold of wild-type) against recombinant mutant molecular clones of HIV-1 expressing nucleoside-resistance mutations including: didanosine resistance (L74V), zalcitabine resistance (T69D), zidovudine resistance (D67N + K70R, D67N + K70R + K219Q, or T215Y) or multinucleoside drug resistance (Q151M complex) mutations in HIV-1 RT.8,75-77

• Tenofovir shows slightly increased activity against HIV-1 expressing the abacavir/lamivudine resistance mutation M184V or the combination of the high-level zidovudine resistance mutation T215Y and M184V.6, 8

• Tenofovir showed activity against all common forms of non-nucleoside-resistant, and protease inhibitor-resistant HIV.8,75-77

• Tenofovir showed a 3 to 4-fold decreased activity against HIV-1 expressing the K65R mutation. K65R was selected by tenofovir in vitro and infrequently by other antiretroviral drugs in vivo.8

• HIV expressing the multinucleoside-resistant T69S double amino acid insertion mutations (T69S Ins) were resistant to tenofovir.78,79 Intermediate susceptibility to tenofovir was observed when these insertions were combined with M184V.

• The removal of nucleoside chain-terminator inhibitors by HIV RT using a pyrophosphate acceptor molecule or a similar mechanism using ATP as an acceptor have been proposed as mechanisms of nucleoside RT resistance.80,81 Tenofovir was inefficiently removed by the ATP-dependent unblocking mechanism by both wild-type RT and an RT mutant with the ZDV resistance mutations D67N + K70R + T215Y that demonstrated increased removal of zidovudine and stavudine.82
4.2.2. Study 902 Virology Substudy

A virology substudy of study 902 included all patients who enrolled in the trial (n= 189); final analyses consisted of the ITT population (n= 186). Both the HIV-1 RT and protease genes from banked plasma samples from all patients were genotypically analyzed at baseline, week 24, week 48, or early termination. Phenotypic analyses of tenofovir susceptibility were performed at baseline and week 48 or early termination for all patients who were assigned to tenofovir DF 300 mg. Additional phenotypic analyses were performed for patients who developed nucleoside-associated RT mutations, including all patients who developed the K65R mutation in RT.

Baseline HIV genotypic data were obtained from 184 of 186 patients in the ITT population; plasma HIV from two patients, both in the placebo arm, failed to generate a sufficient PCR product for genotypic analysis. As noted in Table 4-3, 94% of analyzed patients had plasma HIV expressing one or more primary nucleoside-associated resistance mutations in RT (Resistance Collaborative Group definition),72 57% expressed primary PI-associated resistance mutations, and 32% expressed primary NNRTI-associated resistance mutations. Most patients (74%) had HIV with typical ZDV/thymidine analog-associated resistance mutations at RT codons 41, 67, 70, 210, 215 or 219 (mean of 2.8 mutations); 66% had HIV with the lamivudine/abacavir-associated M184V/I mutations; and 47% had both of these types of resistance mutations.

4.2.2.1. HIV RNA Response to Tenofovir DF Therapy by Baseline HIV Genotype

The HIV RNA responses among patients with HIV expressing specific types of resistance mutations at baseline are shown in Table 4-14 in an intent-to-treat analysis (excluding two patients without baseline genotypic data). The decrease in plasma HIV RNA among patients taking tenofovir DF 300 mg was similar among patients expressing or not expressing ZDV- or lamivudine-associated (M184V) resistance mutations in their HIV. Patients with HIV expressing the M184V mutation in the absence of ZDV-associated mutations had the largest decline in HIV RNA among all genotypic groups (-0.91 log_{10} copies/mL DAVG_{24} for tenofovir DF 300 mg). These responses were durable through 48 weeks of therapy. Patients with HIV expressing the high-level ZDV resistance mutation T215Y or F (51% of patients), NNRTI-associated, or PI-associated resistance mutations also responded durably to tenofovir DF 300 mg. Results of an As-Treated analysis were similar.
Table 4-14. HIV RNA Responses by Baseline Resistance Mutations in Study 902 (N = 184, Virology Intent-to-Treat\( ^1 \))

<table>
<thead>
<tr>
<th>Baseline Mutation Group</th>
<th>Mean DAVG(_{24}^2) (n)</th>
<th>Mean DAVG(_{48}^2,4) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>TDF 75 mg</td>
</tr>
<tr>
<td>All Patients</td>
<td>+0.02 (28)(^1)</td>
<td>-0.26 (53)</td>
</tr>
<tr>
<td>No M184V</td>
<td>+0.28 (10)</td>
<td>-0.32 (15)</td>
</tr>
<tr>
<td>M184V</td>
<td>-0.20 (16)</td>
<td>-0.23 (38)</td>
</tr>
<tr>
<td>M184V/No ZDV-R(^6)</td>
<td>+0.07 (4)</td>
<td>-0.31 (13)</td>
</tr>
<tr>
<td>No ZDV-R(^6)</td>
<td>+0.19 (6)</td>
<td>-0.30 (16)</td>
</tr>
<tr>
<td>ZDV-R(^6)</td>
<td>-0.30 (20)</td>
<td>-0.24 (37)</td>
</tr>
<tr>
<td>ZDV-R(^6)/No M184V</td>
<td>+0.24 (8)</td>
<td>-0.32 (12)</td>
</tr>
<tr>
<td>ZDV-R(^6)+M184V</td>
<td>-0.29 (12)</td>
<td>-0.20 (25)</td>
</tr>
<tr>
<td>T215Y/F</td>
<td>-0.03 (14)</td>
<td>-0.16 (25)</td>
</tr>
<tr>
<td>T215Y/F/No M184V</td>
<td>+0.29 (6)</td>
<td>-0.21 (9)</td>
</tr>
<tr>
<td>T215Y/F+M184V</td>
<td>-0.27 (8)</td>
<td>-0.13 (16)</td>
</tr>
<tr>
<td>T69D/N</td>
<td>-0.53 (5)</td>
<td>-0.15 (9)</td>
</tr>
<tr>
<td>L74V/I</td>
<td>+0.09 (7)</td>
<td>-0.36 (6)</td>
</tr>
<tr>
<td>NNRTI-R(^7)</td>
<td>+0.23 (8)</td>
<td>-0.24 (14)</td>
</tr>
<tr>
<td>Protease Inhibitor-R(^8)</td>
<td>-0.03 (18)</td>
<td>-0.29 (27)</td>
</tr>
</tbody>
</table>

\(^1\) Excluding 2 patients without baseline genotypic data.
\(^2\) Average HIV RNA change from baseline through week 24 (DAVG\(_{24}\)) or week 48 (DAVG\(_{48}\)) in log\(_{10}\) copies/mL.
\(^3\) Wilcoxon rank sum test comparing TDF 300 mg to placebo in the same mutation group.
\(^4\) During weeks 24 through 48, placebo patients received TDF 300 mg, precluding placebo comparisons.
\(^5\) Includes two patients without baseline genotypic data.
\(^6\) Zidovudine resistance mutations are M41L, D67N, K70R, L210W, T215Y/F or K219Q in RT.
\(^7\) K103N or Y181C in RT.
\(^8\) Any amino acid substitution at codons 30, 48, 50, 82, 84, or 90 in protease.

Data from reference: 83

Fewer patients had HIV expressing mutations at other nucleoside-associated RT resistance residues, which precluded definitive analyses of the effects of these mutations on response to therapy with tenofovir DF. There was only a single patient whose HIV expressed the K65R
RT mutation at baseline in this study. Thus, in this study, it is not possible to determine the effect of a pre-existing K65R mutation on response to tenofovir DF therapy.

4.2.2.2. Development of RT Mutations

Post-baseline genotypic data (week 24, week 48, or early termination) were obtained from 159 of 186 patients who received study medication (110 patients at week 48); the remaining patients had insufficient HIV RNA to genotype (n = 27).

**Development of Nucleoside-Associated RT Mutations by Treatment Arm**

Any patient with a post-baseline plasma sample showing a mutation resulting in any amino acid substitution at any of the 16 amino acid residues in RT associated with nucleoside resistance (Resistance Collaborative Group definition; residues 41, 62, 65, 67, 69, 70, 74, 75, 77, 115, 116, 151, 184, 210, 215 and 219 of RT) was considered to have developed a nucleoside-associated RT mutation. Of the 159 genotypically evaluable patients, 79 patients developed one or more of the mutations during the 48-week study.

The distribution of patients who developed nucleoside-associated RT mutations across the placebo and three treatment arms of the study is shown in Table 4-15. During the placebo-controlled phase, 14% of patients in the placebo arm developed a nucleoside-associated RT mutation versus 21%, 37%, and 22% of patients in the tenofovir DF 75 mg, 150 mg, and 300 mg treatment arms, respectively. From logistic regression analyses using the Wald chi-squared test and from Fisher's exact test comparisons, there were no statistically significant differences in the development of nucleoside-associated RT mutations between placebo and each of the treatment arms. Similarly, in patients developing RT mutations through 48 weeks, there was no dose-response across the treatment arms with 34%, 57%, and 39% of patients developing a new nucleoside-associated RT mutation in the three dose groups originally randomized to tenofovir DF therapy. These comparisons suggest that background antiretroviral therapy and not tenofovir DF was responsible for the development of these mutations. Moreover, patients in this study who developed nucleoside-associated RT mutations in the tenofovir DF 300 mg treatment group showed continued viral load suppression in HIV RNA at both week 24 and week 48 (DAVG<sub>24</sub> = -0.59 log<sub>10</sub> copies/mL and DAVG<sub>48</sub> = -0.59 log<sub>10</sub> copies/mL, n = 21) similar to the -0.62 log<sub>10</sub> copies/mL decrease in DAVG<sub>48</sub> observed for all patients treated with tenofovir DF 300 mg (n = 54) or the -0.63 log<sub>10</sub> copies/mL DAVG<sub>48</sub> decrease observed for patients not developing a nucleoside-associated RT mutation (n = 33).
### Table 4-15. Development of Nucleoside-Associated RT Mutations by Treatment Arm in Study 902

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Placebo</th>
<th>TDF 75 mg</th>
<th>TDF 150 mg</th>
<th>TDF 300 mg</th>
<th>p-Value&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients Developing RT Mutations by Week 24 (Number of Patients)</td>
<td>14% (4/28)</td>
<td>21% (11/53)</td>
<td>37% (19/51)</td>
<td>22% (12/54)</td>
<td>0.34</td>
</tr>
<tr>
<td>% of Patients Developing RT Mutations by Week 48 (Number of Patients)</td>
<td>NA (18/53)</td>
<td>34% (29/51)</td>
<td>57% (21/54)</td>
<td>39% (21/54)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

1. Logistic regression analysis and Wald chi-squared test comparing placebo to tenofovir DF (week 24) or across tenofovir DF doses (week 48).
2. At week 24, patients in the placebo arm began receiving TDF 300 mg treatment.

Data from reference: 83

**Development of ZDV/Thymidine Analog-Associated RT Mutations**

The specific amino acid substitutions observed among the patients who developed nucleoside-associated RT mutations also suggest that background therapy was responsible for the development of these mutations (Table 4-16). The majority of the patients (63 of 79) developed typical ZDV-associated mutations while taking either zidovudine, stavudine, abacavir, or lamivudine concomitantly, and the majority of these patients (48 of 63) were adding additional ZDV-associated mutations onto a background of pre-existing ZDV resistance mutations. The capacity of stavudine and abacavir to also select for “zidovudine-associated” mutations in vivo has been established.84-88
### Table 4-16. Development of Antiretroviral-Associated HIV Mutations by Week 48 (Intent-to-Treat, N = 186) in Study 902

<table>
<thead>
<tr>
<th>RT and Protease Resistance Mutations Developing</th>
<th>Percent of Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo ¹ (N = 28)</td>
</tr>
<tr>
<td></td>
<td>Up to Week 24</td>
</tr>
<tr>
<td></td>
<td>Week 24 to 48</td>
</tr>
<tr>
<td>Nucleoside-Associated: (concomitant ART)</td>
<td>14% (4)</td>
</tr>
<tr>
<td>M41L, D67N/G, K70R, L210W/S, T215Y/F/I or K219E/Q/N (d4T, ZDV, ABC or 3TC)</td>
<td>11% (3)</td>
</tr>
<tr>
<td>M184V (3TC)</td>
<td>4% (1)</td>
</tr>
<tr>
<td>T69D/N (ZDV, ABC or d4T)</td>
<td>6% (3)</td>
</tr>
<tr>
<td>L74V/I (ddI, ABC or 3TC)</td>
<td>4% (2)</td>
</tr>
<tr>
<td>K65R (ddI or ABC)</td>
<td>4% (1)</td>
</tr>
<tr>
<td>A62V (ZDV or d4T)</td>
<td>4% (1)</td>
</tr>
<tr>
<td>V75L/A (ddI or d4T)</td>
<td>4% (1)</td>
</tr>
<tr>
<td>Y115F (ABC)</td>
<td>4% (2)</td>
</tr>
<tr>
<td>F77L (ZDV)</td>
<td></td>
</tr>
<tr>
<td>Q151M (ABC and d4T)</td>
<td></td>
</tr>
<tr>
<td>Primary NNRTI-Associated</td>
<td>7% (2)</td>
</tr>
<tr>
<td>(any change at residues 103 or 181 in RT)</td>
<td>¹ ¹</td>
</tr>
<tr>
<td>Primary PI-Associated</td>
<td>11% (3)</td>
</tr>
<tr>
<td>(any change at residues 30, 32, 48, 82, 84, or 90 in protease)</td>
<td>¹ ¹</td>
</tr>
</tbody>
</table>

¹ Patients on placebo up to week 24, TDF 300 mg between weeks 24 and 48.
² 48 of these patients also had ZDV-associated mutations at codons 41, 67, 70, 210, 215, or 219 at baseline.
³ 5 of these patients also had primary NNRTI-associated resistance mutations at baseline.
⁴ 11 of these patients also had primary PI-associated resistance mutations at baseline.

Data from reference: 83
Development of K65R RT Mutations

Four patients (2% of all patients) developed the K65R mutation, an RT mutation associated with zalcitabine, didanosine, and abacavir in vivo, and also selected by tenofovir in vitro. All four patients were taking either didanosine (n = 3) or abacavir (n = 1) concomitantly with tenofovir DF (150 mg or 300 mg). Phenotypic analysis of HIV from all four patients was performed and compared to the patient’s baseline HIV susceptibility to tenofovir. Recombinant HIV from the analyzed patients demonstrated a 2.8 to 3.9-fold reduction in tenofovir susceptibility after the acquisition of the K65R mutation, consistent with results from site-directed recombinant viruses expressing only the K65R mutation. Finally, there was no consistent pattern of HIV RNA increases observed coincident with the development of K65R in the patients.

4.2.2.3. Baseline Phenotypic Analyses

Baseline phenotypic analyses were attempted for all patients treated with tenofovir DF 300 mg at study entry (n = 54); successful phenotypic results were generated for 53 of these patients. Among these 53 patients with baseline phenotypic results, the mean baseline susceptibility was 1.9 fold above wild-type control for tenofovir (range 0.4 - 6.0) versus > 13.8-fold above wild-type for ZDV (range 0.3 - > 150) and > 24.1-fold above wild-type control for lamivudine (range 0.2 - > 54.5). There were a total of four patients who had HIV with > 4-fold reduced susceptibility to tenofovir, including the single patient with the K65R, whose HIV demonstrated 5.2-fold reduced susceptibility to tenofovir. No patients had HIV with > 10-fold reduced susceptibility to tenofovir at baseline.

The HIV RNA response among various strata of baseline susceptibility to tenofovir is shown in Table 4-17. Patients with baseline tenofovir susceptibility within three-fold of wild-type all responded with ≥ 0.5 \( \log_{10} \) decreases in HIV RNA which were durable through week 48. In the intent-to-treat analyses, patients with 3- to 4-fold reduced susceptibility to tenofovir responded to tenofovir DF 300 mg therapy (-0.55 \( \log_{10} \) copies/mL DAVG24 ITT, -0.32 \( \log_{10} \) copies/mL DAVG24 AT). There were only four patients with > 4-fold reduced susceptibility to tenofovir at baseline and, as a group, these patients did not appear to respond to tenofovir DF 300 mg therapy.
Table 4-17.  
Response to Tenofovir DF 300 mg Therapy by Baseline Tenofovir Susceptibility in Study 902

<table>
<thead>
<tr>
<th>Baseline Tenofovir Susceptibility (fold change from wild-type)</th>
<th>N</th>
<th>DAVG$_{24}^1$</th>
<th>DAVG$_{48}^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.0</td>
<td>14</td>
<td>-0.71</td>
<td>-0.61</td>
</tr>
<tr>
<td>&gt; 1.0 and ≤ 2.0</td>
<td>21</td>
<td>-0.63</td>
<td>-0.68</td>
</tr>
<tr>
<td>&gt; 2.0 and ≤ 3.0</td>
<td>8</td>
<td>-0.57</td>
<td>-0.56</td>
</tr>
<tr>
<td>&gt; 3.0 and ≤ 4.0</td>
<td>6</td>
<td>-0.55</td>
<td>-0.55</td>
</tr>
<tr>
<td>&gt; 4.0</td>
<td>4</td>
<td>-0.17</td>
<td>-0.72</td>
</tr>
<tr>
<td>All Patients Analyzed</td>
<td>53</td>
<td>-0.60</td>
<td>-0.63</td>
</tr>
</tbody>
</table>

1 Mean DAVG$_{24}$ for all patients in group (log$_{10}$ copies/mL).

Data from reference: 83

4.2.3.  
Study 907 Virology Substudy

Approximately 50% of enrolled patients were randomly selected and included in the genotypic analyses substudy (n = 274) and 50% of these patients were included in the phenotypic analyses substudy (n = 137). Both the HIV-1 RT and protease genes from banked plasma samples from the patients in the genotyping substudy were genotypically analyzed at baseline and week 24 or early termination. Phenotypic analyses of susceptibility to tenofovir and all approved nucleoside analogs were performed at baseline and week 24 or early termination for all patients in the phenotyping substudy. Baseline HIV genotypic data were obtained from 253 of the 274 patients in the virology genotyping substudy; plasma HIV from 21 patients (14 tenofovir DF; 7 placebo) failed to yield a sufficient PCR product for genotypic analysis.

As noted in Table 4-18, 94% of analyzed patients had plasma HIV expressing one or more primary nucleoside-associated resistance mutations in RT (Resistance Collaborative Group definition), 58% expressed primary PI-associated resistance mutations, and 48% expressed primary NNRTI-associated resistance mutations. Most patients (69%) had HIV with typical ZDV/thymidine analog-associated resistance mutations at RT codons 41, 67, 70, 210, 215, or 219 (mean of 2.8 mutations); 68% had HIV with the lamivudine/abacavir-associated M184V/I mutations; and 45% had both of these types of resistance mutations. The prevalence of each of these baseline resistance mutations is similar across the two treatment arms in the study.
### Table 4-18.  
Baseline Genotypic Analysis in Study 907 (N = 253, Virology Intent-to-Treat)

<table>
<thead>
<tr>
<th>RT and Protease Resistance Mutations at Baseline</th>
<th>Placebo (N = 84)</th>
<th>Tenofovir DF (N = 169)</th>
<th>Total (N = 253)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside-Associated</strong>:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZDV-R (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N)</td>
<td>94% (79)</td>
<td>94% (159)</td>
<td>94% (238)</td>
</tr>
<tr>
<td>M184V/I</td>
<td>64% (54)</td>
<td>70% (118)</td>
<td>68% (172)</td>
</tr>
<tr>
<td>T215Y/F</td>
<td>46% (39)</td>
<td>47% (80)</td>
<td>47% (119)</td>
</tr>
<tr>
<td>M184V/I + ZDV-R</td>
<td>45% (38)</td>
<td>44% (75)</td>
<td>45% (113)</td>
</tr>
<tr>
<td>T69D/N</td>
<td>17% (14)</td>
<td>12% (20)</td>
<td>13% (34)</td>
</tr>
<tr>
<td>L74V/I</td>
<td>11% (9)</td>
<td>9% (15)</td>
<td>9% (24)</td>
</tr>
<tr>
<td>A62V</td>
<td>1% (1)</td>
<td>3% (15)</td>
<td>2% (6)</td>
</tr>
<tr>
<td>V75T/I</td>
<td>1% (1)</td>
<td>2% (4)</td>
<td>2% (5)</td>
</tr>
<tr>
<td>K65R</td>
<td>3% (5)</td>
<td>3% (5)</td>
<td>2% (5)</td>
</tr>
<tr>
<td>Q151M</td>
<td>2% (2)</td>
<td>1% (2)</td>
<td>2% (4)</td>
</tr>
<tr>
<td>T69S Insertions</td>
<td>0% (0)</td>
<td>1% (2)</td>
<td>1% (2)</td>
</tr>
<tr>
<td><strong>Primary NNRTI-Associated</strong></td>
<td>52% (44)</td>
<td>46% (77)</td>
<td>48% (121)</td>
</tr>
<tr>
<td><strong>Primary PI-Associated</strong></td>
<td>62% (52)</td>
<td>57% (96)</td>
<td>58% (148)</td>
</tr>
</tbody>
</table>

2. NNRTI resistance mutations are K103N, V106A, V108I, Y181C/I, Y188C/L/H, G190A/S/E or P236L in RT.
3. Protease inhibitor resistance mutations are D30N, V32I, G48V, I50V, V92A/F/T/S, I84V or L90M in protease.

Data from reference: 92

#### 4.2.3.1.  
HIV RNA Response to Tenofovir DF Therapy by Baseline HIV Genotype

The HIV RNA responses among patients with HIV expressing specific types of resistance mutations at baseline are shown in Table 4-19 in an intent-to-treat analysis. In both intent-to-treat and as-treated analyses, treatment with tenofovir DF resulted in statistically significant decreases in plasma HIV RNA among patients expressing ZDV-associated or lamivudine (M184V)-associated resistance mutations in their HIV. There appeared to be slightly
improved responses in patients expressing the M184V mutation versus those without M184V, and slightly diminished response in patients expressing ZDV-associated mutations in their HIV versus those without ZDV-associated mutations, but the net treatment differences were not statistically significant.92

Table 4-19. HIV RNA Responses by Baseline Resistance Mutations in Study 907 (N = 253, Virology Intent-to-Treat)

<table>
<thead>
<tr>
<th>Baseline Mutation Group</th>
<th>Mean DAVG$_{24}^{1}$ (n)</th>
<th>Net Treatment Effect $^{2}$</th>
<th>P-Value $^{3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>-0.03 (84)</td>
<td>-0.59 (168)</td>
<td>-0.56</td>
</tr>
<tr>
<td>No M184V</td>
<td>+0.02 (30)</td>
<td>-0.40 (51)</td>
<td>-0.42</td>
</tr>
<tr>
<td>M184V</td>
<td>-0.05 (54)</td>
<td>-0.68 (117)</td>
<td>-0.63</td>
</tr>
<tr>
<td>M184V / No ZDV-R$^{4}$</td>
<td>-0.16 (16)</td>
<td>-0.97 (42)</td>
<td>-0.81</td>
</tr>
<tr>
<td>No ZDV-R$^{4}$</td>
<td>-0.18 (23)</td>
<td>-0.85 (54)</td>
<td>-0.67</td>
</tr>
<tr>
<td>ZDV-R$^{4}$</td>
<td>+0.03 (61)</td>
<td>-0.47 (114)</td>
<td>-0.50</td>
</tr>
<tr>
<td>ZDV-R$^{4}$ / No M184V</td>
<td>+0.09 (23)</td>
<td>-0.39 (39)</td>
<td>-0.48</td>
</tr>
<tr>
<td>ZDV-R$^{4}$ + M184V</td>
<td>-0.01 (39)</td>
<td>-0.51 (75)</td>
<td>-0.50</td>
</tr>
<tr>
<td>T215Y/F</td>
<td>+0.05 (39)</td>
<td>-0.32 (80)</td>
<td>-0.37</td>
</tr>
<tr>
<td>T215Y/F / No M184V</td>
<td>+0.08 (18)</td>
<td>-0.31 (33)</td>
<td>-0.39</td>
</tr>
<tr>
<td>T215Y/F + M184V</td>
<td>+0.01 (21)</td>
<td>-0.32 (47)</td>
<td>-0.33</td>
</tr>
<tr>
<td>T69D/N</td>
<td>+0.08 (14)</td>
<td>-0.42 (20)</td>
<td>-0.50</td>
</tr>
<tr>
<td>I74V/I</td>
<td>+0.13 (9)</td>
<td>-0.22 (15)</td>
<td>-0.35</td>
</tr>
<tr>
<td>K65R</td>
<td>0</td>
<td>+0.12 (5)</td>
<td>+0.12</td>
</tr>
<tr>
<td>Q151M</td>
<td>+0.05 (2)</td>
<td>+0.38 (2)</td>
<td>+0.33</td>
</tr>
<tr>
<td>T69S Insertions</td>
<td>0</td>
<td>+0.29 (2)</td>
<td>+0.29</td>
</tr>
<tr>
<td>NNRTI-R$^{4}$</td>
<td>+0.02 (44)</td>
<td>-0.49 (77)</td>
<td>-0.51</td>
</tr>
<tr>
<td>Protease Inhibitor-R$^{4}$</td>
<td>-0.00 (52)</td>
<td>-0.55 (96)</td>
<td>-0.55</td>
</tr>
</tbody>
</table>

1 Average HIV RNA change from baseline through week 24 (DAVG$_{24}$) in log$_{10}$ copies/mL.
2 Difference between DAVG$_{24}$ values of tenofovir DF- versus placebo-treated patients.
3 Wilcoxon rank sum test comparing tenofovir DF to placebo in the same mutation group.
4 Zidovudine resistance mutations are M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N in RT.
5 NNRTI resistance mutations are K103N, V106A, V108I, Y181C/I, Y188C/L/H, G190A/S/E or P236L in RT.
6 Protease inhibitor resistance mutations are D30N, V32I, G48V, 150V, V82A/F/T/S, I84V or L90M in protease.
7 Not applicable; no comparator patients in placebo arm.

Data from reference: 92
Patients with HIV expressing the M184V mutation in the absence of ZDV-associated mutations had the largest decline in HIV RNA among all genotypic groups (-0.97 log_{10} copies/mL DAVG_{24}). Patients with HIV expressing the high-level ZDV resistance mutation T215Y or F (47\% of patients), NNRTI-associated, or PI-associated resistance mutations also responded significantly to tenofovir DF therapy. In addition, patients who expressed the less common nucleoside-associated RT mutations T69N/D, associated with zalcitabine and other nucleoside therapies, or L74V/I, associated with didanosine or abacavir therapy, also responded significantly to tenofovir DF therapy.

At baseline, five patients had HIV expressing the K65R RT mutation, a mutation associated with reduced susceptibility to tenofovir from \textit{in vitro} studies, but also selected by abacavir and didanosine \textit{in vivo}. These five patients were all randomly assigned to tenofovir DF therapy and did not respond to tenofovir DF therapy (+0.12 log_{10} copies/mL mean DAVG_{24}). Fewer patients assigned to tenofovir DF had HIV expressing mutations at the multinucleoside drug resistance site Q151M (n=2) or the multinucleoside resistance insertion mutation after codon T69 (n=2). Neither of these groups responded to tenofovir DF therapy with mean DAVC_{24} values of +0.38 log_{10} copies/mL and +0.29 log_{10} copies/mL, respectively. The small numbers of patients and the lack of placebo controls in these genotypic groups, however, preclude conclusive determination of the effects of these mutations on response to therapy with tenofovir DF.

4.2.3.2. Development of Mutations

Post-baseline genotypic data (week 24 or early termination) were obtained from 171 of 274 patients in the genotypic analyses substudy, with the remaining patients having insufficient HIV RNA to genotype (n=102) or no post-baseline plasma sample (n=1). Proportionally fewer patients in the tenofovir DF treatment arm (54\%) than in the placebo arm (80\%) had week 24 genotypic results due to a greater number of tenofovir DF treated patients who had insufficient HIV RNA for analysis.

Forty-seven patients developed one or more RT mutations at known nucleoside-associated resistance sites during the first 24 weeks (Table 4-20). Slightly fewer patients in the tenofovir DF treatment arm than in the placebo arm developed nucleoside-associated RT mutations (15\% vs. 22\%, respectively, p = 0.17, Fisher's exact test). Development of NNRTI-associated mutations were less common, but also occurred less frequently in the tenofovir DF arm (5\% vs. 9\%, p = 0.17). Significantly fewer patients developed PI-associated mutations in the tenofovir DF arm than in the placebo arm (2\% vs. 8\%, respectively, p = 0.02, Fisher's exact test). Thus, it appears that tenofovir DF therapy was contributing to the suppression of nucleoside-, NNRTI- and PI-associated mutation development, consistent with significant decreases in viral load observed among tenofovir DF-treated patients.
## Table 4-20.
Development of Antiretroviral-Associated HIV Mutations by Week 24 in Study 907 (Genotyping Substudy, N = 274)

<table>
<thead>
<tr>
<th>RT and Protease Resistance Mutations Developing</th>
<th>Concomitant Nucleoside ART</th>
<th>Percent of Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside-Associated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M41L</td>
<td>d4T, ZDV, ddl, ABC, 3TC</td>
<td>22% (20)</td>
</tr>
<tr>
<td>K70R/Q/N</td>
<td>d4T, ZDV, ddl, ABC, 3TC</td>
<td>15% (27)</td>
</tr>
<tr>
<td>D67N</td>
<td>d4T, ZDV, ddl, ABC, 3TC</td>
<td>17% (47)</td>
</tr>
<tr>
<td>T215Y/F/I</td>
<td>d4T, ZDV, ddl, ABC, 3TC</td>
<td>13% (12)</td>
</tr>
<tr>
<td>L74V/I</td>
<td>d4T, ddl, ABC, 3TC</td>
<td>10% (19)</td>
</tr>
<tr>
<td>K65R</td>
<td>d4T, ZDV, ddl, ABC, 3TC</td>
<td>11% (31)</td>
</tr>
<tr>
<td>K219E/Q/R</td>
<td>d4T, ZDV, ddl, ABC, 3TC</td>
<td>3% (2)</td>
</tr>
<tr>
<td>L210W/S</td>
<td>d4T, ddl</td>
<td>1% (2)</td>
</tr>
<tr>
<td>M184V</td>
<td>ZDV, ABC, 3TC</td>
<td>1% (2)</td>
</tr>
<tr>
<td>T69N/I</td>
<td>d4T, ddl</td>
<td>2% (2)</td>
</tr>
<tr>
<td>V75I/A</td>
<td>d4T, ddl, ABC</td>
<td>1% (7)</td>
</tr>
<tr>
<td>A62V</td>
<td>ZDV, 3TC</td>
<td>1% (7)</td>
</tr>
<tr>
<td>Y115F</td>
<td>d4T, ABC, 3TC</td>
<td>1% (7)</td>
</tr>
<tr>
<td>Q151M</td>
<td>d4T, ABC, 3TC</td>
<td>1% (7)</td>
</tr>
<tr>
<td><strong>Primary NNRTI-Associated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9% (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary PI-Associated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8% (7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Zidovudine resistance mutations are M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N in RT.
2 22 of these patients also had ZDV-associated mutations at codons 41, 67, 70, 210, 215, or 219 at baseline (10 placebo, 12 TDF).
3 NNRTI resistance mutations are K103N, V106A, V108I, Y181C/I, Y188C/L/H, G190A/S/E, or P236L in RT.
4 11 of these patients also had primary NNRTI-associated resistance mutations at baseline (6 placebo, 5 TDF).
5 Protease inhibitor resistance mutations are D30N, V32I, G48V, I50V, V82A/F/T/S, I84V, or L90M in protease.
6 7 of these patients also had primary PI-associated resistance mutations at baseline (6 placebo, 1 TDF).

Data from reference: 92
Development of Nucleoside-Associated RT Mutations

The majority of the patients (31 of 47) who developed nucleoside-associated mutations developed typical ZDV-associated mutations while taking zidovudine, stavudine, abacavir, or didanosine concomitantly. The capacity of stavudine, abacavir and didanosine to also select for "zidovudine-associated" mutations in vivo has been established.84-88 There were no significant differences in the development of any of the ZDV-associated RT mutations between patients in the placebo and tenofovir DF arms of the study. Development of the D67N mutation appeared to occur more frequently in the tenofovir DF arm, but this was also not statistically significant (p = 0.28, Fisher’s exact test). Among the seven patients who developed a D67N mutation, there was continued viral load suppression (-0.94 log10 copies/mL DAVG24). Overall, the concomitant use of antiretroviral agents known to select for ZDV-associated mutations and their similar distribution between the treatment arms suggests that the concomitant antiretroviral agents were primarily responsible for their development.

Patients who developed nucleoside-associated RT mutations in the tenofovir DF treatment group showed continued viral load suppression in HIV RNA at week 24 (-0.51 log10 copies/mL DAVG24, n = 27) similar to the -0.60 log10 copies/mL decrease in DAVG24 observed for all patients treated with tenofovir DF in the virology substudy. Moreover, using the secondary endpoint of absolute change in HIV RNA from baseline, tenofovir DF treated patients who developed nucleoside-associated RT mutations during the first 24 weeks still showed a statistically significant mean HIV RNA decrease of -0.41 log10 copies/mL through week 24, suggesting continued anti-HIV activity despite the development of these mutations.92

Development of K65R RT Mutations

Five patients (2% of all patients, 3% of tenofovir DF treated patients) developed the K65R mutation, an RT mutation associated with zalcitabine, didanosine and abacavir in vivo, and also selected by tenofovir in vitro.75,89-91 All five patients were in the tenofovir DF treatment arm. Two of these patients were taking either didanosine or abacavir concomitantly, and three were taking lamivudine concomitantly along with tenofovir DF. Among these five patients, there was a notable variation in their response to tenofovir DF therapy, with a mean DAVG24 of -0.29 log10 copies/mL (range: -1.10 to +0.72). Overall, few patients developed the K65R mutation and there was no consistent pattern of HIV RNA increases observed coincident with its development that would reflect treatment failure.

Development of Other Nucleoside-Associated RT Mutations

Fifteen patients developed one or more RT mutations at the other nucleoside-associated resistance codons (62, 69, 74, 75, 115, 151 or 184), and the emergence of substitutions at these codons was correlated with use of concomitant nucleoside analogs previously shown to select for these mutations (didanosine, stavudine, abacavir, zidovudine and lamivudine). The concomitant antiretroviral therapies that patients were taking are listed in Table 4-20. At
..each of these RT residues, a new mutation developed in less than 3% of patients and there was a similar distribution between the tenofovir DF and placebo treatment arms. A single patient developed a mutation associated with multinucleoside drug resistance (Q151M) while taking tenofovir DF, but also stavudine and abacavir concomitantly. The capacity of stavudine to potentially select for the Q151M multinucleoside resistance complex has been described.\textsuperscript{86-88} No patient developed an insertion mutation near codon T69 in plasma HIV during this study.

4.2.3.3. Baseline Phenotypic Analyses

Baseline phenotypic analyses were attempted for all patients randomly assigned into the virology phenotyping substudy (n=137) with the Virco Antivirogram\textsuperscript{TM} assay; successful phenotypic results were generated for 85 of these patients (56 tenofovir DF, 29 placebo). Among these 85 patients, the mean number of ZDV-associated resistance mutations was 2.1 and the mean number of NRTI-associated resistance mutations was 3.2. Overall, the mean baseline susceptibility was 1.7-fold above wild-type control for tenofovir versus 7.6-fold above wild-type for ZDV and >31.8-fold above wild-type for lamivudine. There were a total of nine patients who had HIV with >4-fold reduced susceptibility to tenofovir. None of these nine patients had the K65R mutation at baseline, but had multiple nucleoside-associated mutations (mean = 4.8). No patient had HIV with >10-fold reduced susceptibility to tenofovir at baseline as compared to wild-type HIV.

The HIV RNA response among various strata of baseline susceptibility to tenofovir is shown in Table 4-21. In intent-to-treat analyses, patients with baseline tenofovir susceptibility within 3-fold of wild-type responded with -0.42 to -0.72 log\textsubscript{10} copies/mL decreases in HIV RNA through week 24. There were few patients within the other phenotypic strata, but there appeared to be a reduction in response consistent with the linear regression modeling. There were only five patients in the tenofovir DF arm with >4-fold reduced susceptibility to tenofovir at baseline and, as a group, these patients did not appear to respond to tenofovir DF therapy.
Table 4-21. Response to Tenofovir DF Therapy by Baseline Tenofovir Susceptibility in Study 907

<table>
<thead>
<tr>
<th>Baseline Tenofovir Susceptibility (fold change from wild-type)</th>
<th>Tenofovir DF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean DAVG(_{24}) (n)</td>
<td>Mean DAVG(_{24}) (n)</td>
</tr>
<tr>
<td></td>
<td>Intent-to-Treat</td>
<td>As-Treated</td>
</tr>
<tr>
<td>≤ 1.0</td>
<td>-0.72 (25)</td>
<td>-0.74 (25)</td>
</tr>
<tr>
<td>&gt; 1.0 and ≤ 2.0</td>
<td>-0.50 (17)</td>
<td>-0.50 (17)</td>
</tr>
<tr>
<td>&gt; 2.0 and ≤ 3.0</td>
<td>-0.42 (6)</td>
<td>-0.36 (6)</td>
</tr>
<tr>
<td>&gt; 3.0 and ≤ 4.0</td>
<td>-0.27 (3)</td>
<td>-0.27 (3)</td>
</tr>
<tr>
<td>&gt; 4.0</td>
<td>-0.08 (5)</td>
<td>-0.08 (5)</td>
</tr>
<tr>
<td>All Patients Analyzed</td>
<td>-0.54 (56)</td>
<td>-0.54 (56)</td>
</tr>
</tbody>
</table>

1 Mean DAVG\(_{24}\) for all patients in group (log\(_{10}\) copies/mL).

Data from reference: 92

4.2.4. Cross-Study Virology Analyses

Further evaluation of the antiviral response in patients with specific thymidine analog mutations (M41L, D67N, K70R, L210W, T215 Y/F, and K219Q) was undertaken using combined data from studies 902 and 907. In these analyses, the presence of either M41L or L210W mutation in combination with 3 other thymidine analog mutations predicted a reduced response to therapy.

4.2.5. Virology Conclusions

In conjunction with the clinical trials, virology substudies were conducted in over 400 patients treated with tenofovir DF and the results support the in vitro and preclinical studies. In an integrated analysis of these virology substudies, the following conclusions can be made:

- Tenofovir DF once daily showed significant and durable HIV RNA reductions in patients with HIV expressing:
  - Zidovudine/thymidine analog resistance mutations
  - The M184V lamivudine resistance mutation
  - The T215Y high-level zidovudine resistance mutation
- NNRTI- and PI-associated resistance mutations
- Combinations of these resistance mutations

Baseline phenotypic analyses demonstrated that:

- 90% of antiretroviral-experienced patients had HIV with susceptibility to tenofovir within 4-fold of wild-type and these patients responded to tenofovir DF treatment.

- Patients with up to 10-fold zidovudine resistance and > 30-fold lamivudine resistance responded to tenofovir DF therapy. A subgroup of patients with > 10-fold zidovudine resistance showed diminished responses to tenofovir DF therapy.

- Diminished responses to tenofovir DF therapy were observed in patients with > 4-fold reduced susceptibility to tenofovir at baseline. These patients had either the K65R RT mutation, a T69S double insertion mutation, or the T215Y/F and multiple other RT resistance mutations (mean 4.8) in their baseline HIV.

- Treatment of HIV-infected patients with tenofovir DF for up to 48 weeks is associated with infrequent development of resistance to tenofovir DF:
  - Nine patients developed the K65R RT mutation (2.4% of treated patients).
  - Development was not associated with an increase in plasma HIV RNA.
  - No evidence for the development of novel resistance mutations from genotypic or phenotypic analyses was observed.

- Treatment with tenofovir DF was associated with a reduction in the development of NRTI-associated, or primary NNRTI-associated or PI-associated resistance mutations (study 907).

- Development of zidovudine/thymidine analog-associated mutations:
  - Occurred similarly in the placebo and tenofovir DF arms.
  - Appeared to be due to the patients' concomitant nucleoside therapy.
  - Did not result in loss of viral load suppression.

- Reduced responses were noted in patients with either an M41L or L210W mutation in combination with 3 other thymidine analog mutations.

In summary, treatment with tenofovir DF results in:
Tenofovir Disoproxil Fumarate
FDA Briefing Document
NDA 21-356

- Significant antiviral efficacy through 24 - 48 weeks in highly antiretroviral-experienced patients with extensive nucleoside resistance in HIV at baseline.

- Low incidence of genotypic or phenotypic resistance to tenofovir arising during 24 - 48 weeks of tenofovir DF therapy.

- Reduction in the incidence of resistance mutations associated with nucleoside RT inhibitors, non-nucleoside RT inhibitors or protease inhibitors.

- Continued viral load suppression in patients who develop nucleoside-associated RT mutations.

4.3. Safety

Safety data from the Integrated Summary of Safety and from the Safety Update are summarized in this section. The Integrated Summary of Safety was included in the NDA submission (01 May 2001). The Safety Update was submitted to the FDA on 15 August 2001.

For the Integrated Summary of Safety data from studies 902 and 907 were pooled. A total of 149 patients in study 902 and 538 patients in study 907 received at least one dose of tenofovir DF 300 mg. As of 01 May 2001, 368 patients from study 907, 101 patients from study 902 and 6 patients from study 901 had rolled over to study 910. For the Safety Update, data from studies 902, 907, and rollover protocol 910 were pooled for the safety evaluation.

4.3.1. Treatment Duration (Exposure)

4.3.1.1. Pooled Studies (902, 907, 910)

In the pooled data from studies 902, 907, and 910, the mean duration of treatment in those patients who received at least one dose of tenofovir DF 300 mg is approximately 58 weeks (range: 0.4 to 143 weeks) as of the safety update data cut-off. Mean treatment duration described in the NDA was 36 weeks. See Table 4-22.

<table>
<thead>
<tr>
<th>Table 4-22. Treatment Duration (Pooled Studies)</th>
<th>NDA</th>
<th>Safety Update</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NDA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo (0-24 Weeks)</td>
<td>TDF 300 mg (0-24 Weeks)</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>210</td>
<td>443</td>
</tr>
<tr>
<td>Weeks on Study Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>23.0 ± 4.0</td>
<td>23.0 ± 4.1</td>
</tr>
<tr>
<td>Median</td>
<td>24.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Range</td>
<td>2.1 to 25.9</td>
<td>0.4 to 29.3</td>
</tr>
</tbody>
</table>
4.3.2. Patient Disposition

4.3.2.1. Pooled Studies (902, 907, 910)

A total of 687 patients received tenofovir DF 300 mg either initially or through rollover from another dose group. Figure 4-7 graphically presents the disposition of patients enrolled in studies 902 and 907. Most patients who completed studies 902 or 907 continued on tenofovir DF treatment in study 910.

Reasons for discontinuation for patients enrolled in studies 902, 907, and 910 are summarized in Table 4-23. The frequency of premature study discontinuation remains low despite prolonged treatment with tenofovir DF. In the All Tenofovir DF group, 29 patients (4%) discontinued tenofovir DF 300 mg due to adverse events or intercurrent illness, by the NDA data cutoff. As of the safety update cut-off, 44 patients (6%) had discontinued. Fifteen patients (2%) were lost to follow-up.

Figure 4-7. Patient Disposition - Safety Population (Patients Originally Enrolled in 902 and 907 Only)

Note: The 6 patients from study 901 who rolled over into study 910 are not included.
Table 4-23. Disposition of Study Patients (Pooled Studies)

<table>
<thead>
<tr>
<th></th>
<th>NDA</th>
<th>Safety Update</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (0-24 Weeks) (N = 210)</td>
<td>All TDF (N = 687)</td>
</tr>
<tr>
<td>Mean Duration (± SD) of Treatment (Weeks)</td>
<td>23.0 ± 4.0</td>
<td>35.8 ± 30.4</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Received at Least One Dose of Study Drug/TDF 300 mg</td>
<td>210</td>
<td>100%</td>
</tr>
<tr>
<td>Discontinued Prematurely</td>
<td>18</td>
<td>9%</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>6</td>
<td>3%</td>
</tr>
<tr>
<td>Lack of Virologic Response</td>
<td>3</td>
<td>1%</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>4</td>
<td>2%</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Other&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4</td>
<td>2%</td>
</tr>
</tbody>
</table>

1 Other reasons for discontinuation include investigator decision, patient request, prohibited concomitant medications, or not specified.
4.3.3. Treatment Discontinuation for Adverse Events and Laboratory Abnormalities

4.3.3.1. Pooled Studies (902, 907, 910)

Overall, the incidence of adverse events or laboratory abnormalities leading to discontinuation of tenofovir DF has remained low despite mean treatment durations of more than one year, and extending to nearly three years in some patients.

In the pooled studies, 35 patients (5%) who received at least one dose of tenofovir DF 300 mg discontinued study treatment due to adverse events. This is slightly higher than the 3% for this group reported in the NDA and the 2% reported for the 24-week placebo group (Table 4-24). No individual adverse event requiring study drug discontinuation occurred in more than 1% of patients. The most frequent event leading to discontinuation was nausea (7 patients, 1%). All other adverse events leading to study drug discontinuation occurred at frequencies less than 1%.

One percent of tenofovir DF-treated patients discontinued treatment due to laboratory abnormalities. Individual laboratory abnormalities that led to study treatment discontinuation occurred in less than 1% of patients (Table 4-25).
### Table 4-24. Discontinuation Due to Adverse Events in Pooled Studies

<table>
<thead>
<tr>
<th>Events</th>
<th>NDA Placebo (0-24 Weeks) (N = 210)</th>
<th>TDF 300 mg (0-24 Weeks) (N = 443)</th>
<th>All TDF (N = 687)</th>
<th>Safety Update All TDF (N = 687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Duration (± SD) of Treatment (Weeks)</td>
<td>23.0 ± 4.0</td>
<td>23.0 ± 4.1</td>
<td>35.8 ± 30.4</td>
<td>58.2 ± 31.9</td>
</tr>
<tr>
<td>Patients Who Discontinued Due to Adverse Events</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>3 1%</td>
<td>6 1%</td>
<td>9 1%</td>
<td>15 2%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
<td>2 &lt;1%</td>
<td>3 &lt;1%</td>
</tr>
<tr>
<td>Malaise</td>
<td>0 0%</td>
<td>0 0%</td>
<td>0 0%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Pain</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
</tr>
<tr>
<td>Headache</td>
<td>1 &lt;1%</td>
<td>0 0%</td>
<td>0 0%</td>
<td>0 0%</td>
</tr>
<tr>
<td>Abdomen Enlarged</td>
<td>0 0%</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
</tr>
<tr>
<td>Hernia</td>
<td>0 0%</td>
<td>0 0%</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
</tr>
<tr>
<td>Digestive</td>
<td>2 &lt;1%</td>
<td>7 2%</td>
<td>8 1%</td>
<td>14 2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 &lt;1%</td>
<td>4 &lt;1%</td>
<td>5 &lt;1%</td>
<td>7 1%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0 0%</td>
<td>0 0%</td>
<td>0 0%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 &lt;1%</td>
<td>2 &lt;1%</td>
<td>2 &lt;1%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0 0%</td>
<td>0 0%</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
</tr>
<tr>
<td>Eruption</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
</tr>
</tbody>
</table>

(Continued on next page)
Table 4-24. Discontinuation Due to Adverse Events in Pooled Studies (Continued)

<table>
<thead>
<tr>
<th>Event</th>
<th>NDA Placebo (0-24 Weeks) (N = 210)</th>
<th>TDF 300 mg (0-24 Weeks) (N = 443)</th>
<th>All TDF (N = 687)</th>
<th>Safety Update All TDF (N=687)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Intestinal Obstruction</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1</td>
<td>&lt;1%</td>
<td>1</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hematologic and Lymphatic</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Metabolic and Nutritional</td>
<td>2</td>
<td>&lt;1%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>&lt;1%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1</td>
<td>&lt;1%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Lactic Acidosis</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>SGOT Increased</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>SGPT Increased</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>0</td>
<td>0%</td>
<td>2</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Peripheral Neuritis</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0</td>
<td>0%</td>
<td>2</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

(Continued on next page)
Table 4-24. Discontinuation Due to Adverse Events in Pooled Studies (Continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>NDA Placebo (0-24 Weeks)</th>
<th>TDF 300 mg (0-24 Weeks)</th>
<th>All TDF (N = 687)</th>
<th>Safety Update (N=687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalitis</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Carcinoma of Lung</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Sputum Increased</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Voice Alteration</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Urogenital</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Breast Enlargement</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Urinary Frequency</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Impotence</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Skin</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Scborrhea</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Table 4-25. Discontinuation Due to Laboratory Abnormalities in Pooled Studies

<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>ISS Placebo (0-24 Weeks)</th>
<th>TDF 300 mg (0-24 Weeks)</th>
<th>All TDF (N = 687)</th>
<th>Safety Update All TDF (N = 687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Duration (± SD) of Treatment (Weeks)</td>
<td>23.0 ± 4.0</td>
<td>23.0 ± 4.1</td>
<td>35.8 ± 30.4</td>
<td>58.2 ± 31.9</td>
</tr>
<tr>
<td>Patients Who Discontinued Due to Laboratory Abnormalities</td>
<td>n  %</td>
<td>n  %</td>
<td>n  %</td>
<td>n  %</td>
</tr>
<tr>
<td>Creatine Kinase Increased</td>
<td>2  &lt;1%</td>
<td>2  &lt;1%</td>
<td>8  1%</td>
<td>12  1%</td>
</tr>
<tr>
<td>AST Increased</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
<td>2  &lt;1%</td>
<td>5  &lt;1%</td>
</tr>
<tr>
<td>ALT Increased</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
<td>1  &lt;1%</td>
<td>4  &lt;1%</td>
</tr>
<tr>
<td>Triglycerides Increased</td>
<td>2  &lt;1%</td>
<td>0  0%</td>
<td>2  &lt;1%</td>
<td>2  &lt;1%</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>0  0%</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
<td>2  &lt;1%</td>
</tr>
<tr>
<td>Serum Amylase Increased</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
<td>1  &lt;1%</td>
<td>1  &lt;1%</td>
</tr>
<tr>
<td>Lipase Increased</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
<td>1  &lt;1%</td>
<td>1  &lt;1%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0  0%</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
<td>1  &lt;1%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0  0%</td>
<td>0  0%</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>0  0%</td>
<td>0  0%</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>0  0%</td>
<td>0  0%</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>0  0%</td>
<td>0  0%</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
</tr>
<tr>
<td>Alkaline Phosphatase Increased</td>
<td>0  0%</td>
<td>0  0%</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>0  0%</td>
<td>0  0%</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>0  0%</td>
<td>0  0%</td>
<td>1  &lt;1%</td>
<td>1  &lt;1%</td>
</tr>
</tbody>
</table>

Note: Patients may have discontinued due to more than one event.
4.3.4. Adverse Events

Table 4-26 below summarizes all adverse events reported in the pooled studies at a frequency of 5% or greater in either of the tenofovir treatment groups as of the NDA data cut-off.

Most patients experienced one or more adverse events. Comparing the placebo and tenofovir DF 300 mg 24-week treatment groups, a slightly higher incidence of gastrointestinal events (for example, diarrhea, nausea, and vomiting) was observed among tenofovir DF-treated patients. There was a statistically significant higher incidence of vomiting (12% vs. 6%, p = 0.0225) in the tenofovir DF 300 mg group compared with the placebo group. However, no adjustments for multiple comparisons were made. Importantly, < 1% of patients discontinued treatment with tenofovir DF due to these gastrointestinal events.

A significantly higher incidence of increased cough (9% vs. 4%, p = 0.0226) was reported in the tenofovir DF 300 mg group in the placebo-controlled periods of the pooled studies compared to placebo. Examination of the episodes of increased cough revealed that they occurred throughout the course of treatment in these studies and were uniformly associated with other symptoms of respiratory infection or seasonal allergic disorder. Therefore, it seems unlikely that increased cough would be attributed to treatment with tenofovir DF.

In the All Tenofovir DF group, which includes patients with longer durations of treatment, the most commonly reported adverse events were headache and non-specific systemic complaints such as asthenia, pain and viral infections, respiratory complaints of pharyngitis, rhinitis and sinusitis, gastrointestinal symptoms of nausea, diarrhea and vomiting, and rash. Importantly, the frequencies of adverse events in this group of patients were not notably higher than those observed during 24-weeks of treatment.
### Table 4-26. Adverse Events Reported in ≥ 5% of TenofovirDF-Treated Patients in Pooled Studies – ISS

<table>
<thead>
<tr>
<th></th>
<th>Placebo (0 – 24 Weeks)</th>
<th>TDF 300 mg (0 – 24 Weeks)</th>
<th>All TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Duration (± SD) of Treatment (Weeks)</td>
<td>23.0 ± 4.0</td>
<td>23.0 ± 4.1</td>
<td>35.8 ± 30.4</td>
</tr>
<tr>
<td>Number of Patients Treated</td>
<td>210</td>
<td>443</td>
<td>687</td>
</tr>
<tr>
<td>Number of Patients Experiencing Adverse Events</td>
<td>187 (89%)</td>
<td>397 (90%)</td>
<td>523 (76%)</td>
</tr>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>35 (17%)</td>
<td>83 (19%)</td>
<td>127 (18%)</td>
</tr>
<tr>
<td>Headache</td>
<td>30 (14%)</td>
<td>61 (14%)</td>
<td>103 (15%)</td>
</tr>
<tr>
<td>Pain</td>
<td>34 (16%)</td>
<td>54 (12%)</td>
<td>99 (14%)</td>
</tr>
<tr>
<td>Viral Infection</td>
<td>19 (9%)</td>
<td>46 (10 %)</td>
<td>84 (12%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>16 (8%)</td>
<td>43 (10%)</td>
<td>72 (10%)</td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>9 (4%)</td>
<td>21 (5%)</td>
<td>52 (8%)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>13 (6%)</td>
<td>26 (6%)</td>
<td>50 (7%)</td>
</tr>
<tr>
<td>Fever</td>
<td>8 (4%)</td>
<td>21 (5%)</td>
<td>42 (6%)</td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>7 (3%)</td>
<td>28 (6%)</td>
<td>46 (7%)</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (17%)</td>
<td>96 (22%)</td>
<td>154 (22%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (15 %)</td>
<td>89 (20%)</td>
<td>136 (20%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (6%)</td>
<td>51 (12%)</td>
<td>81 (12%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>10 (5%)</td>
<td>26 (6%)</td>
<td>47 (7%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>8 (4%)</td>
<td>29 (7%)</td>
<td>45 (7%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4 (2%)</td>
<td>27 (6%)</td>
<td>40 (6%)</td>
</tr>
<tr>
<td><strong>Hematologic and Lymphatic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>4 (2%)</td>
<td>15 (3%)</td>
<td>31 (5%)</td>
</tr>
<tr>
<td><strong>Metabolic and Nutritional</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Loss</td>
<td>7 (3%)</td>
<td>19 (4%)</td>
<td>44 (6%)</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>16 (8%)</td>
<td>22 (5%)</td>
<td>37 (5%)</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>13 (6%)</td>
<td>24 (5%)</td>
<td>48 (7%)</td>
</tr>
<tr>
<td>Depression</td>
<td>14 (7%)</td>
<td>25 (6%)</td>
<td>47 (7%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13 (6%)</td>
<td>29 (7%)</td>
<td>53 (8%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 (7%)</td>
<td>16 (4%)</td>
<td>31 (5%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6 (3%)</td>
<td>16 (4%)</td>
<td>31 (5%)</td>
</tr>
</tbody>
</table>

*(Continued on following page)*
### Table 4-26. Adverse Events Reported in $\geq 5\%$ of Tenofovir DF-Treated Patients in the Pooled 902 and 907 Studies (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (0 - 24 Weeks)</th>
<th>TDF 300 mg (0 - 24 Weeks)</th>
<th>All TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>32 (15%)</td>
<td>78 (18%)</td>
<td>144 (21%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>23 (11%)</td>
<td>41 (9%)</td>
<td>89 (13%)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>18 (9%)</td>
<td>52 (12%)</td>
<td>91 (13%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6 (3%)</td>
<td>15 (3%)</td>
<td>31 (5%)</td>
</tr>
<tr>
<td>Cough Increased</td>
<td>8 (4%)</td>
<td>39 (9%)</td>
<td>67 (10%)</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>17 (8%)</td>
<td>39 (9%)</td>
<td>72 (10%)</td>
</tr>
<tr>
<td>Sweating</td>
<td>5 (2%)</td>
<td>25 (6%)</td>
<td>45 (7%)</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>7 (3%)</td>
<td>18 (4%)</td>
<td>33 (5%)</td>
</tr>
</tbody>
</table>

Note: A patient may be reported in more than one category.

### 4.3.5. Grade 3 or 4 Adverse Events

Grade 3 or 4 adverse events with a frequency of $\geq 1\%$ are summarized in Table 4-27, as of the NDA data cut-off. The incidence of Grade 3 or 4 adverse events was low and similar for the placebo and tenofovir DF groups through 24 weeks. In the All Tenofovir DF group, frequencies did not increase compared to the 24-week data.

### Table 4-27. Grade 3 or 4 Adverse Events Reported in $\geq 1\%$ of Tenofovir DF-Treated Patients in the Pooled Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo (0 - 24 Weeks)</th>
<th>TDF 300 mg (0 - 24 Weeks)</th>
<th>All TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Duration (± SD) of Treatment (Weeks)</strong></td>
<td>23.0 ± 4.0</td>
<td>23.0 ± 4.1</td>
<td>35.8 ± 30.4</td>
</tr>
<tr>
<td>Number of Patients Treated</td>
<td>210</td>
<td>443</td>
<td>687</td>
</tr>
<tr>
<td>Number of Patients Who Experienced Grade 3 or 4 Adverse Events</td>
<td>28 (13%)</td>
<td>62 (14%)</td>
<td>110 (16%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>21 (10%)</td>
<td>56 (13%)</td>
<td>92 (13%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>7 (3%)</td>
<td>6 (1%)</td>
<td>18 (3%)</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (&lt; 1%)</td>
<td>3 (&lt; 1%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2 (&lt; 1%)</td>
<td>3 (&lt; 1%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (&lt; 1%)</td>
<td>3 (&lt; 1%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (1%)</td>
<td>4 (&lt; 1%)</td>
<td>7 (1%)</td>
</tr>
</tbody>
</table>

Note: A patient may be reported in more than one category.
4.3.6. **Marked Laboratory Abnormalities**

Table 4-28 displays frequency of marked abnormalities for selected laboratory parameters among patients in the pooled studies. Marked laboratory abnormality is defined as a shift from grade 0 at baseline to at least grade 3 during study or from grade 1 at baseline to grade 4 during study.

Marked laboratory abnormalities occurred with similar frequencies in the placebo and the tenofovir DF groups during the 24-week blinded periods of the pooled studies and did not appear to increase with longer durations of treatment in the All Tenofovir DF group. The frequencies of marked changes of individual laboratory abnormalities were similar in all of the groups. Among all tenofovir DF-treated patients, 11 patients were identified who had marked changes in ALT, including three with chronic hepatitis B or C. Three patients had a concomitant increase in serum total bilirubin. All three of the bilirubin increases were Grade 1 in severity.

Elevations in ALT were significantly associated with the presence of underlying hepatitis. From the available data, there does not appear to be evidence of significant hepatotoxicity associated with tenofovir DF.

### Table 4-28. Selected Marked Laboratory Abnormalities (Pooled Studies)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (0 - 24 Weeks)</th>
<th>TDF 300 mg (0 - 24 Weeks)</th>
<th>All TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Duration (± SD) of Treatment (Weeks)</strong></td>
<td>23.0 ± 4.0</td>
<td>23.0 ± 4.1</td>
<td>35.8 ± 30.4</td>
</tr>
<tr>
<td><strong>Number of Patients Treated</strong></td>
<td>210</td>
<td>443</td>
<td>687</td>
</tr>
<tr>
<td><strong>Number of Patients Experiencing Marked Laboratory Toxicity by Highest Grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>18 (9%)</td>
<td>41 (9%)</td>
<td>73 (11%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>13 (6%)</td>
<td>21 (5%)</td>
<td>42 (6%)</td>
</tr>
<tr>
<td><strong>Hypertriglyceridemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0 → Grade 3</td>
<td>5 (2%)</td>
<td>6 (1%)</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Grade 0 → Grade 4</td>
<td>1 (&lt; 1%)</td>
<td>3 (&lt; 1%)</td>
<td>8 (1%)</td>
</tr>
<tr>
<td><strong>Hypophosphatemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0 → Grade 3</td>
<td>1 (&lt; 1%)</td>
<td>0 (0%)</td>
<td>1 (&lt; 1%)</td>
</tr>
<tr>
<td>Grade 0 → Grade 4</td>
<td>0 (0%)</td>
<td>1 (&lt; 1%)</td>
<td>1 (&lt; 1%)</td>
</tr>
<tr>
<td><strong>Creatine Kinase</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0 → Grade 3</td>
<td>2 (&lt; 1%)</td>
<td>9 (2%)</td>
<td>26 (4%)</td>
</tr>
<tr>
<td>Grade 0 → Grade 4</td>
<td>6 (3%)</td>
<td>11 (2%)</td>
<td>20 (3%)</td>
</tr>
<tr>
<td>Grade 1 → Grade 4</td>
<td>3 (1%)</td>
<td>2 (&lt; 1%)</td>
<td>3 (&lt; 1%)</td>
</tr>
</tbody>
</table>
Table 4-28. Selected Marked Laboratory Abnormalities (Pooled Studies) (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (0 – 24 Weeks)</th>
<th>TDF 300 mg (0 – 24 Weeks)</th>
<th>All TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0 → Grade 3</td>
<td>1 (&lt; 1%)</td>
<td>5 (1%)</td>
<td>8 (1%)</td>
</tr>
<tr>
<td>Grade 0 → Grade 4</td>
<td>0 (0%)</td>
<td>1 (&lt; 1%)</td>
<td>3 (&lt; 1%)</td>
</tr>
<tr>
<td>Grade 1 → Grade 4</td>
<td>1 (&lt; 1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>AST</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0 → Grade 3</td>
<td>1 (&lt; 1%)</td>
<td>9 (2%)</td>
<td>18 (3%)</td>
</tr>
<tr>
<td>Grade 0 → Grade 4</td>
<td>0 (0%)</td>
<td>1 (&lt; 1%)</td>
<td>3 (&lt; 1%)</td>
</tr>
<tr>
<td><strong>Serum Amylase</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0 → Grade 3</td>
<td>4 (2%)</td>
<td>7 (2%)</td>
<td>13 (2%)</td>
</tr>
<tr>
<td>Grade 0 → Grade 4</td>
<td>0 (0%)</td>
<td>1 (&lt; 1%)</td>
<td>1 (&lt; 1%)</td>
</tr>
<tr>
<td><strong>Glycosuria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0 → Grade 3</td>
<td>4 (2%)</td>
<td>9 (2%)</td>
<td>13 (2%)</td>
</tr>
</tbody>
</table>

Note: Marked laboratory abnormality is defined as a shift from grade 0 at baseline to at least grade 3 during study or from grade 1 at baseline to grade 4 during study.

4.3.7. Serious Adverse Events

4.3.7.1. Pooled Studies (902, 907, 910)

During the first 24 weeks of treatment in the placebo-controlled studies 902 and 907, the incidence of serious adverse events was higher in the placebo-treated patients (8%) compared to those who received tenofovir DF (5%).

As of the data cut-off for the safety update, among all patients who received at least one dose of tenofovir DF 300 mg in these studies, the incidence of SAEs was 13%. Among these patients, only two events (pneumonia, 2%, and pancreatitis, 1%) occurred at frequencies ≥ 1%. All other events occurred in less than 1% of patients treated.

As noted in the NDA, the incidence of serious adverse events in the pooled studies judged to be possibly or probably related to tenofovir DF was low (less than 1%). As of the data cut-off for the safety update, one new possibly/probably related case (pancreatitis) had been reported.

During the 24-week placebo-controlled periods of studies 902 and 907, the incidence of serious adverse events was higher in placebo recipients compared to those patients who received tenofovir DF. With extended treatment duration, the incidence of serious adverse events increased somewhat, but individual events occurred infrequently, with only
pneumonia and pancreatitis occurring in 1% or more of patients. The cases of pneumonia were judged to be not related to tenofovir DF. Among all cases of pancreatitis in the pooled studies (7 patients, 1%), 2 cases were judged to be related to tenofovir DF. Serious adverse events judged related to study drug were uncommon, reported in less than 1% of treated patients.
Table 4-29. Serious Adverse Events in Pooled Studies (>1 Patient)

<table>
<thead>
<tr>
<th>Serious Adverse Events by Body System</th>
<th>Placebo (0-24 Weeks) (N = 210)</th>
<th>TDF 300 mg (0-24 Weeks) (N = 443)</th>
<th>All TDF (Safety Update) (N = 687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Duration (± SD) of Treatment (Weeks)</td>
<td>23.0 ± 4.0</td>
<td>23.0 ± 4.1</td>
<td>58.2 ± 31.9</td>
</tr>
<tr>
<td>Number of Patients Who Experienced Any Serious Adverse Event</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>15 7%</td>
<td>18 4%</td>
<td>89 13%</td>
</tr>
<tr>
<td>Bacterial Infection</td>
<td>4 2%</td>
<td>4 &lt;1%</td>
<td>22 3%</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
<td>6 &lt;1%</td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>1 &lt;1%</td>
<td>2 &lt;1%</td>
<td>3 &lt;1%</td>
</tr>
<tr>
<td>Abscess</td>
<td>0 0%</td>
<td>0 0%</td>
<td>3 &lt;1%</td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Fever</td>
<td>1 &lt;1%</td>
<td>0 0%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0 0%</td>
<td>0 0%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
<td>8 1%</td>
</tr>
<tr>
<td>Digestive</td>
<td>3 1%</td>
<td>6 1%</td>
<td>19 3%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0 0%</td>
<td>2 &lt;1%</td>
<td>7 1%</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 &lt;1%</td>
<td>0 0%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 0%</td>
<td>0 0%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Metabolic and Nutritional</td>
<td>2 &lt;1%</td>
<td>2 &lt;1%</td>
<td>5 &lt;1%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>0 0%</td>
<td>0 0%</td>
<td>2 &lt;1%</td>
</tr>
</tbody>
</table>

(Continued on next page)
<table>
<thead>
<tr>
<th>Serious Adverse Events by Body System</th>
<th>Placebo (0-24 Weeks) (N = 210)</th>
<th>TDF 300 mg (0-24 Weeks) (N = 443)</th>
<th>All TDF (Safety Update) (N = 687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients Who Experienced Any Serious Adverse Event</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>17 8%</td>
<td>23 5%</td>
<td>89 13%</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>3 1%</td>
<td>1 &lt;1%</td>
<td>12 2%</td>
</tr>
<tr>
<td>Fracture</td>
<td>1 &lt;1%</td>
<td>0 0%</td>
<td>6 &lt;1%</td>
</tr>
<tr>
<td>Joint Disorder</td>
<td>2 &lt;1%</td>
<td>0 0%</td>
<td>4 &lt;1%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>2 &lt;1%</td>
<td>1 &lt;1%</td>
<td>14 2%</td>
</tr>
<tr>
<td>Depression</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
<td>3 &lt;1%</td>
</tr>
<tr>
<td>Cerebrovascular Accident</td>
<td>0 0%</td>
<td>0 0%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0 0%</td>
<td>3 &lt;1%</td>
<td>20 3%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0 0%</td>
<td>2 &lt;1%</td>
<td>12 2%</td>
</tr>
<tr>
<td>Lung Disorder</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
<td>3 &lt;1%</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Asthma</td>
<td>0 0%</td>
<td>0 0%</td>
<td>2 &lt;1%</td>
</tr>
<tr>
<td>Skin</td>
<td>1 &lt;1%</td>
<td>1 &lt;1%</td>
<td>3 &lt;1%</td>
</tr>
<tr>
<td>Urogenital</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
<td>11 2%</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>0 0%</td>
<td>1 &lt;1%</td>
<td>3 &lt;1%</td>
</tr>
<tr>
<td>Kidney Calculus</td>
<td>0 0%</td>
<td>0 0%</td>
<td>3 &lt;1%</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>0 0%</td>
<td>0 0%</td>
<td>2 &lt;1%</td>
</tr>
</tbody>
</table>
4.3.8. **Targeted Evaluation of Renal and Bone Parameters**

Based on preclinical studies, bone and kidney were identified as potential target organs for toxicity. Further evaluation of parameters specific to these two organs is provided in this section.

4.3.8.1. **Serum Creatinine and Serum Phosphorus**

Serum creatinine abnormalities were uncommon in the central laboratory database; no patient had a serum creatinine elevation above grade 1 (Table 4-30). Despite extended treatment duration, in the All Tenofovir DF group at the safety update data cut-off, 5% of patients had grade 1 creatinine elevations. Of the 32 patients with grade 1 creatinine elevations, 18 (3%) had serum creatinines ≥ 1.5 mg/dL, with a maximum of 1.9 mg/dL.

Fifteen percent of patients in the All Tenofovir DF group had grade 1 or 2 hypophosphatemia reported as of the safety update cut-off (Table 4-31). There were 4 patients who were reported to have grade 3 or 4 hypophosphatemia. One patient with grade 3 toxicity had this same grade at baseline, and the other three patients (two grade 3, one grade 4) had values within normal limits when the tests were repeated within 10 days of the abnormal finding. The lowest confirmed serum phosphorus value was 1.5 mg/dL.

To evaluate the largely sporadic and transient appearance of hypophosphatemia, an analysis was performed in patients who had ≥ grade 2 hypophosphatemia. Of the 62 patients (All TDF group) who had ≥ grade 2 hypophosphatemia, 51 had an abnormal value at only one visit, with the abnormality resolved by the subsequent visit. Ten patients had two consecutive grade 2 values; only one patient had 3 consecutive grade 2 values. No patient was discontinued from study due to hypophosphatemia.

With extended treatment duration, as of the data cut-off for the safety update, the incidence of serum creatinine elevations (5%) and hypophosphatemia (15%) in the pooled studies increased only slightly compared to the data presented in the NDA (4% and 14%, respectively). No patients had greater than grade 1 serum creatinine elevation or greater than grade 2 hypophosphatemia that was confirmed on retesting.

Serum creatinine elevations and serum phosphate decreases appear to occur sporadically in this patient population, do not worsen, and resolve with treatment interruption. To date, there remains no evidence of a significant tenofovir DF-related effect on these parameters.
### Table 4-30. Maximum Grade of Laboratory Toxicity - Serum Creatinine (Pooled Studies)

<table>
<thead>
<tr>
<th></th>
<th>NDA</th>
<th>Safety Update</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (0-24 Weeks) (N = 210)</td>
<td>TDF 300 mg (0-24 Weeks) (N = 443)</td>
</tr>
<tr>
<td>Mean Duration (± SD) of Treatment (Weeks)</td>
<td>23.0 ± 4.0</td>
<td>23.0 ± 4.1</td>
</tr>
<tr>
<td>Maximum Grade of Laboratory Abnormality</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>Grade 1 (≥ 0.5 mg/dL over BL*)</td>
<td>3 1%</td>
<td>6 1%</td>
</tr>
<tr>
<td>Grade 2 (2.1 – 3.0 mg/dL)</td>
<td>0 0%</td>
<td>0 0%</td>
</tr>
<tr>
<td>Grade 3 (3.1 – 6.0 mg/dL)</td>
<td>0 0%</td>
<td>0 0%</td>
</tr>
<tr>
<td>Grade 4 (&gt; 6.0 mg/dL)</td>
<td>0 0%</td>
<td>0 0%</td>
</tr>
</tbody>
</table>

Note: Grade was missing for one patient in the tenofovir DF 300 mg group.

* BL = Baseline
Table 4-31. Maximum Grade of Laboratory Toxicity - Serum Phosphorus (Pooled Studies)

<table>
<thead>
<tr>
<th>Maximum Grade of Laboratory Abnormality</th>
<th>NDA Placebo (0-24 Weeks) (N = 210)</th>
<th>NDA TDF 300 mg (0-24 Weeks) (N = 443)</th>
<th>NDA All TDF (N = 687)</th>
<th>Safety Update All TDF (N = 687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Duration (± SD) of Treatment (Weeks)</td>
<td>23.0 ± 4.0</td>
<td>23.0 ± 4.1</td>
<td>35.8 ± 30.4</td>
<td>58.2 ± 31.89</td>
</tr>
<tr>
<td>Maximum Grade of Laboratory Abnormality</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Grade 1 (2.0 - 2.2 mg/dL)</td>
<td>10</td>
<td>5%</td>
<td>27</td>
<td>6%</td>
</tr>
<tr>
<td>Grade 2 (1.5 - 1.9 mg/dL)</td>
<td>5</td>
<td>2%</td>
<td>28</td>
<td>6%</td>
</tr>
<tr>
<td>Grade 3 (1.0 - 1.4 mg/dL)</td>
<td>1</td>
<td>&lt;1%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Grade 4 (&lt; 1.0 mg/dL)</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Note: Grade was missing for one patient in the tenofovir DF 300 mg group.
4.3.8.2. Bone Fractures

All adverse events and physical findings reported to the clinical databases for studies 901, 902, 903, 907, 908, and 910 were reviewed, evaluating all verbatim terms for evidence of bone fracture.

4.3.8.2.1. Tenofovir DF Exposure

Table 4-32 details the exposure to tenofovir DF in studies 901, 902, 903, 907, and 908 based on the time of first dose to the last available date recorded on study, inclusive of central laboratory data. Studies 901 extension, 902, and 907 include the time on tenofovir DF for those patients who subsequently rolled over and are now being followed under study 910.

Table 4-32. Tenofovir DF Exposure at Time of Data Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Who Received Tenofovir DF/Placebo</th>
<th>Total Exposure (Person-Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>902 and 907 Placebo Group¹</td>
<td>210</td>
<td>99</td>
</tr>
<tr>
<td>901, 902, 907 (combined)²</td>
<td>727</td>
<td>814</td>
</tr>
<tr>
<td>903³</td>
<td>600</td>
<td>388</td>
</tr>
<tr>
<td>908⁴</td>
<td>291</td>
<td>284</td>
</tr>
</tbody>
</table>

1 Includes 28 and 182 patients from studies 902 and 907, respectively.
2 Includes 10,179, and 538 patients from studies 901, 902, and 907, respectively. Exposure in rollover study 910 is also included in the calculation.
3 Study is still in blinded phase; only overall data are available.
4 Five patients who never received study drug were excluded from the summary.

4.3.8.2.2. Fracture Events

A total of 30 bone fractures, including eleven that were serious adverse events, are reported from the databases for studies 902, 903, 907, 908, and 910. Three of the thirty fractures were in patients receiving placebo in study 907. No fractures have been reported in the Expanded Access Program study 955.

4.3.8.2.3. Fracture Rates

Fracture rates have been calculated and are summarized in Table 4-33 for studies 903, 908, and the pooled data from studies 901, 902, and 907 as well as data from patients who rolled over into study 910. The fracture rate for the pooled data is presented by treatment group. The fracture rates in the tenofovir DF-treated patients are lower than the rate observed among
placebo-treated patients. All fractures were trauma-induced except for one patient with a history of osteoporotic fracture.

### Table 4-33. Fracture Rates in Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Group</th>
<th>Number of Fractures</th>
<th>Fracture Rate¹ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>902 and 907 Placebo Group²</td>
<td>Placebo</td>
<td>3</td>
<td>3.0 (0.6 – 8.9)</td>
</tr>
<tr>
<td>901, 902, 907 (combined)³</td>
<td>Tenofovir DF</td>
<td>16</td>
<td>2.0 (1.1 – 3.2)</td>
</tr>
<tr>
<td>903⁴</td>
<td>Tenofovir DF/ stavudine</td>
<td>4</td>
<td>1.0 (0.3 – 2.6)</td>
</tr>
<tr>
<td>908⁵</td>
<td>Tenofovir DF</td>
<td>7</td>
<td>2.3 (0.8 – 4.9)</td>
</tr>
</tbody>
</table>

¹ Events/100 patient-years
² Includes 28 and 182 patients from studies 902 and 907, respectively.
³ Includes 10, 179, and 538 patients from studies 901, 902, and 907, respectively. Exposure in rollover study 910 is also included in the calculation.
⁴ Study is still in blinded phase; only overall data are available.
⁵ Five patients who never received study drug were excluded from the summary.

### 4.3.9. Study 908

Data from study 908, an open-label safety study that enrolled 296 patients with advanced AIDS (mean baseline CD4 = 36 cells/mL), also support the lack of significant toxicity attributable to tenofovir DF. The frequencies of grade 3 or 4 adverse events were somewhat greater in study 908 compared to the phase 2-3 studies, but the frequencies of individual serious adverse events was similar, and all of the reported deaths were attributed to HIV disease. The frequencies and severities of adverse events in this study are consistent with the advanced disease status of the enrolled patients.

### 4.3.10. Safety Conclusions

The frequency of premature study drug discontinuation is low despite prolonged treatment with tenofovir DF. The incidence of discontinuations due to adverse events or intercurrent illness across the pooled studies is 6%. This rate compares favorably with discontinuation rates for studies of other antiretroviral therapies in similar treatment-experienced patient populations: 3% to 5% in a study of efavirenz and/or nelfinavir and 4% to 9% in a study of lopinavir/ritonavir and nevirapine.

Overall, the incidence of adverse events or laboratory abnormalities leading to discontinuation of tenofovir DF has remained low. In the pooled studies, the incidence has been 5% for adverse events and 1% for laboratory abnormalities.
The incidence of serum creatinine elevations (5%) and hypophosphatemia (15%) in the pooled studies each increased by 1% during additional follow-up since the NDA (from 4% and 14%, respectively). No patients had greater than grade 1 serum creatinine elevations and no patients had greater than grade 2 hypophosphatemia confirmed by a second consecutive measurement. The maximum observed peak serum creatinine in studies 902 and 907 was 1.9 mg/dL; nadir confirmed serum phosphorus was 1.4 mg/dL.

During the 24-week placebo-controlled periods of studies 902 and 907, the incidence of serious adverse events was higher in placebo recipients compared to patients who received tenofovir DF. Although the incidence of serious adverse events increased with extended treatment duration, individual events occurred infrequently - only pneumonia (2%) and pancreatitis (1%) occurred in 1% or more of patients. Related serious adverse events were uncommon, occurring in less than 1% of treated patients.

The incidence of bone fractures in study 908 and in pooled data from studies 902, 907, and 910 are 2.5 and 2.0 events/100 person-years of exposure, respectively. These rates are lower than that observed among patients treated with placebo for 24 weeks in studies 902 and 907 (3.0 events/100 person-years). Analysis of interval fracture rates showed sporadic increases and decreases in fracture rates over time, with no apparent trend. All fractures were trauma-induced except in the case of one patient with a history of osteoporotic fracture.

In conclusion, these safety data confirm that tenofovir DF has been well tolerated among treatment-experienced HIV-infected patients, for treatment durations as long as 143 weeks. There is no apparent evidence of significant drug-related toxicity associated with the use of tenofovir DF.

4.4. Clinical Pharmacokinetics and Metabolism

The pharmacokinetic profile of tenofovir DF has been established following single and multiple dosing of intravenous tenofovir and oral tenofovir DF in HIV-1-infected patients and healthy subjects. The principal findings of the pharmacokinetic studies are:

- In HIV-infected patients, tenofovir pharmacokinetics were dose proportional over a dose range of 75 to 600 mg oral tenofovir DF and there was no clinically relevant change in the PK profile with daily dosing for periods of up to 24 weeks (studies 901 and 907).

- Tenofovir is primarily eliminated renally as unchanged drug with active tubular secretion by the kidney contributing to the elimination profile (studies 701, 901, and 914).

- The terminal half-life of tenofovir (approximately 11-14 hours) is sufficiently long enough to permit once daily dosing (studies 901 and 914).

- The oral bioavailability of tenofovir from tenofovir DF in fasted patients was approximately 25% (study 901). Administration of tenofovir DF with food (high-fat
meal), enhanced the oral bioavailability with an increase in tenofovir AUC by approximately 40% and Cmax by approximately 14% (study 914).

- The pharmacokinetics of tenofovir were unaltered by concomitant administration with a variety of antiretroviral agents that are frequently taken in the HIV-infected population and are known to alter the pharmacokinetics of other medications (study 909). Although a higher serum concentration of didanosine was observed, data from the clinical studies provide no evidence that this interaction is of clinical significance. The slight decrease observed in the plasma concentration of ABT-378 is probably not clinically important.

4.4.1. Tenofovir (IV)

In study 701, the pharmacokinetics of intravenous tenofovir were examined following single and repeated (7 days) administration at two dose levels (1.0 and 3.0 mg/kg) in a total of 16 patients with HIV infection.

Serum concentrations and AUC increased in a dose-proportional manner following single intravenous doses of tenofovir. Concentrations of tenofovir in serum reached an observed maximum of 2.71 μg/mL and 8.52 μg/mL at the 1.0 and 3.0 mg/kg dose levels, respectively. Thereafter, serum concentrations declined in a bi-phasic manner, with an estimated mean terminal half-life of 5.3 hr and 7.8 hr for the 1.0 and 3.0 mg/kg dose levels, respectively. With the exception of the terminal half-life and volume of distribution, the pharmacokinetics of tenofovir were independent of dose over the dose range 1.0 to 3.0 mg/kg following the first dose. The mean renal clearance of tenofovir following the initial dose (~160 mL/hr/kg) exceeded creatinine clearance (~75 mL/hr/kg), indicating active tubular secretion contributes to the elimination profile of tenofovir. Approximately 70% to 80% of the administered tenofovir dose was excreted unchanged in urine within 72 hours following the first dose.

Following once daily dosing for 7 days at the 3.0 mg/kg/day dose level, there was an apparent decrease in serum and renal clearances of tenofovir. These observations may be due to inadequate assessment of the day 1 terminal phase of tenofovir.

4.4.2. Tenofovir DF (Oral) (Studies 901 and 907)

The pharmacokinetics of oral tenofovir DF (75 mg, 150 mg, 300 mg, or 600 mg) and tenofovir DF 75 mg plus hydroxyurea (HU), following single and repeat daily dosing were evaluated in 46 HIV-infected adult patients in study 901. Subjects received a single dose of study drug in the fasted state and, after a seven-day washout period, 28 consecutive daily doses of study drug, each following a meal.

For the 75 mg and 150 mg dose cohorts, concentrations above the limit of quantitation of the bioanalytical assay were few, resulting in limited pharmacokinetic data. Median maximum serum tenofovir concentrations (Cmax) were dose-proportional for the tenofovir DF 75, 150, 300, 600, and 75 mg + HU dosing cohorts at 68.6, 111, 240, 618, and 71.2 ng/mL, respectively. The time to reach maximum concentrations (Tmax) was similar for all doses in
the fasted state (0.5-1.0 hours) and was delayed by 0.8 to 1.2 hours when administered with food. For the 300 mg and 600 mg dose groups, after $C_{\text{max}}$ was achieved, serum tenofovir concentrations declined in a biexponential manner with median terminal half-life values of 11 and 13 hours, respectively, regardless of feeding state or pharmacokinetic visit.

Apparent clearance and renal clearance of tenofovir exceeded calculated creatinine clearance, indicating active tubular secretion of tenofovir by the kidney. Neither serum creatinine nor calculated creatinine clearance were affected by repeated administration (8 to 28 days) of tenofovir DF at any dose level.

Steady-state pharmacokinetic parameters evaluated on day 15 were dose-linear across all dose groups. There were no changes in pharmacokinetic parameters over time as assessed by comparison of total drug exposure following the first dose versus steady state. Tenofovir exposure over the dosing interval at steady-state for the 300 mg and 600 mg doses was similar to the total tenofovir exposure following the first dose.

Oral bioavailability of tenofovir was approximated using historical data obtained in an evaluation of 1 mg/kg intravenous dose. The bioavailability of tenofovir was enhanced by administration of food. Oral bioavailability of tenofovir DF 300 mg and 600 mg doses were estimated as 25% and 21%, respectively, in the fasted state, and as 39% and 34%, respectively, in the fed state. The median steady-state serum tenofovir exposure after 8 consecutive doses of tenofovir DF 150, 300, and 600 mg was 35%, 63%, and 131%, respectively, of that measured following administration of 1 mg/kg intravenous tenofovir.

The pharmacokinetics of tenofovir were also examined in 14 patients enrolled in the pharmacokinetic substudy of study 907. All pharmacokinetic assessments were performed in the fed state with the consumption of a standardized high-fat meal. The pharmacokinetics of tenofovir observed in this patient sample were comparable to those described for the shorter dosing period in study 901. Following the first oral dose of tenofovir DF the median $C_{\text{max}}$ was 213 ng/mL and was achieved 2.4 hours following dosing. Thereafter, concentrations of tenofovir in serum declined in a bi-phasic manner with a median terminal half-life of 13 hours. The AUC₀⁻₈ on day 1 was 2750 ng*hr/mL.

As in study 901, the pharmacokinetics of tenofovir were not affected by repeat dosing. Steady-state pharmacokinetic parameters evaluated on week 12 (n = 7) were consistent with those predicted from day 1 results, indicating that the pharmacokinetics of tenofovir were not time-dependent. There was a small degree of tenofovir accumulation by week 12, consistent with the long serum half-life of tenofovir. Comparison of week 12 and 24 visits (n = 7) revealed no significant changes in tenofovir pharmacokinetics with time. In addition, calculated creatinine clearance was unchanged from day 1 through 12 and 24 weeks of study.

In summary, once daily oral administration of tenofovir DF 300 mg resulted in predictable serum tenofovir pharmacokinetics that were unchanged over 24 weeks of study.
4.4.3. Drug Interactions (Study 909)

Study 909 was a steady-state drug interaction study to assess the pharmacokinetic parameters of tenofovir DF (TDF) when administered alone or in combination with lamivudine (3TC), didanosine (ddI), indinavir (IDV), ABT-378/ritonavir and efavirenz (EFR) in healthy volunteers. For the purpose of examining pharmacokinetic parameters, healthy volunteers were selected for the study population to minimize the confounding effects of background antiretroviral and other therapies as well as the multiple, short-term changes in treatment regimens that may be required in HIV patients.

The study included five cohorts. In each cohort tenofovir DF was paired with either lamivudine, didanosine, indinavir, ABT-378/ritonavir, or efavirenz. All drugs were dosed to steady-state. Tenofovir DF, didanosine, lamivudine, and indinavir were administered for 7 days, while ABT-378/ritonavir and efavirenz were given for 14 days. When administered together with ABT-378/ritonavir or efavirenz, tenofovir DF was also given for 14 days. HIV medications chosen for study have the following pharmacokinetic characteristics:

- Lamivudine and didanosine are renally excreted and could compete with tenofovir for elimination.
- Indinavir inhibits the CYP450 enzyme system responsible for its own metabolism and other protease inhibitor metabolism, as well as the metabolism of many other drugs.
- ABT-378/ritonavir is a potent CYP450 inhibitor and induces the expression of CYP450 enzymes.
- Efavirenz is an inducer of CYP450 enzyme expression and inhibitor the metabolism of compounds metabolized by these enzymes.

Overall, the results of this study demonstrate a lack of clinically significant effects on the pharmacokinetics of tenofovir, when tenofovir DF was administered with other antiretroviral agents. Tenofovir DF had no significant effect on the pharmacokinetics of lamivudine, indinavir or efavirenz. The administration of ABT-378/ritonavir in combination with tenofovir DF caused a statistically significant increase (approximately 30%) in the C_{max} and AUC_{0-\infty} of tenofovir; however, interpretation of this result is difficult. This may be a food effect rather than a drug-drug interaction. Administration of tenofovir DF with didanosine caused a 28% increase in the C_{max} and a 44% increase in the AUC_{0-\infty} of didanosine. An analysis of patients using tenofovir and concomitant didanosine from the pooled dataset of 907 and 902 showed no evidence of an increased frequency of didanosine-related adverse events or laboratory abnormalities (pancreatitis, peripheral neuropathy, elevated amylase or lipase) when didanosine was administered with tenofovir DF. This suggests that the observed drug interaction is unlikely to be clinically significant.

Tenofovir DF also had slight but statistically significant effects on the disposition of ABT-378 causing an approximate 15% decrease in the C_{max} and AUC_{0-\infty} parameters.
However, minimum plasma concentrations of ABT-378 were unaffected. This interaction is probably not clinically important.

4.4.4. **Effect of Food (Study 914)**

This study assessed the effect of food on the intended commercial formulation when administered in the fasted state. Following the first dose of tenofovir DF in fed patients, the mean concentration of tenofovir in serum was 335 ng/mL. The oral bioavailability of tenofovir from tenofovir DF in fasted patients was approximately 25%. Administration of tenofovir DF with food enhanced the oral bioavailability; geometric mean ratios for AUC(0-∞) and AUC₀₋₅ were approximately 40% higher (140% and 138%, respectively), following administration with food. The 90% confidence intervals fell outside the 80% to 125% range, indicating a food effect. When tenofovir DF was administered in the fed state, the mean urinary excretion was higher (23.5%) compared with in the fasted state (16.9%), presumably due to the enhanced bioavailability. Mean renal clearance values were essentially identical in each treatment group. Renal clearance of tenofovir exceeded creatinine clearance indicating elimination via both active secretion and glomerular filtration. The terminal elimination half-life of tenofovir in serum averaged approximately 18 hours in each treatment group, supporting the once daily dosing schedule of tenofovir DF.

4.4.5. **Demographic Effects on the Pharmacokinetics of Tenofovir**

A rank ANOVA model that included factors for HIV-infection, gender, age, and weight was developed to assess the effects and/or potential relationships of demographic variables with the pharmacokinetics of tenofovir using pooled single-dose data from studies 901 (n = 8), 907 (n = 9), and 914 (n = 66).

There were no significant differences in the pharmacokinetics of tenofovir between HIV-infected patients (n = 17) and uninfected subjects (n = 36) (p > 0.1538) with the exception of terminal elimination half-life (p < 0.0001). This difference was likely due to a shorter duration of blood sampling post-dose in HIV-infected patients vs. healthy subjects (24 hours and 48 hours, respectively). There were no significant differences in the pharmacokinetics of tenofovir between females and males (p > 0.2559) or effect due to age (19 to 57 years) or body weight (p > 0.4305). There was insufficient data available from racial groups other than Caucasian to investigate potential pharmacokinetic differences among these populations. However, there do not appear to be substantial differences between races with regard to tenofovir pharmacokinetics.

There were no statistically significant differences in the pharmacokinetics of tenofovir due to gender, age, or body weight. There was insufficient data available from non-Caucasian patients to investigate potential pharmacokinetic differences among these populations; however, there do not appear to be substantial differences between races.
5. PLANS FOR FURTHER DEVELOPMENT

A number of additional studies are underway or are planned as part of the tenofovir DF clinical development program.

5.1. Study 903

A confirmatory double-blind active-controlled phase 3 study (study 903) designed to support traditional approval is ongoing, evaluating the safety and efficacy of tenofovir DF versus stavudine, both in combination with efavirenz and lamivudine in HIV-1-infected patients with plasma HIV-1 RNA levels > 5,000 copies/mL who are antiretroviral therapy-naïve. The enrolled patient population is 74% male with an average age of 35 years. Mean baseline HIV-1 RNA is 4.90 log_{10} copies/mL (range: 2.60 - 6.49), and mean baseline CD4 count is 277 cells/mm³ (range: 3 - 1071). The study is fully accrued with 601 patients and 48-week data are expected to become available in early 2002. The study will continue blinded for 96 weeks, providing long-term, controlled safety and efficacy data.

5.2. Study 928

Study 928 will be a second 48-week confirmatory study conducted in treatment-experienced, failing pediatric patients. The proposed design includes a blinded, placebo-controlled, 2-week evaluation of tenofovir DF as add-on therapy followed by optimization of background therapy and continuation of the blinded, placebo-controlled evaluation of tenofovir DF. A pediatric-appropriate formulation, currently in development, will be utilized in this study, scheduled to begin in March 2002.

5.3. Study 910

As described previously, study 910 is a rollover protocol for patients who were receiving tenofovir DF in extended dosing phases of studies 901, 902, and 907. Study 910 will continue through December 2002, thereby permitting the continued collection of safety data from patients with the longest exposure to tenofovir DF.

5.4. Study 917

A small, short-term (3-week) pilot study (study 917) to evaluate the viral dynamics of tenofovir DF 300 mg given once daily as monotherapy in a group of treatment-naïve HIV-1-infected patients has been initiated. This study will provide additional data regarding the antiviral potency of tenofovir DF.
5.5. Expanded Access

Expanded Access Programs are underway in the U.S., Europe, Canada, and Australia. These programs are intended to provide tenofovir DF for patients with advanced HIV disease in need of a new antiretroviral agent and to collect long-term safety data in this population.

5.6. Collaborations

In addition to Gilead-sponsored studies, tenofovir DF 300 mg is included in the treatment regimens of a number of ongoing and planned collaborative studies. One, an Abbott-sponsored study conducted by Martin Markowitz, M.D. at the Aaron Diamond Center (M00-154; study 916), which began enrollment in late 2000, is an observational, 48-week, open-label study of complete viral suppression in antiretroviral-naïve patients. A second, a GlaxoSmithKline study (ESS 40006; study 918), which began enrollment in June 2000, is a randomized, open-label, 48-week study for patients with virologic evidence of treatment failure. Both of these studies will provide long-term efficacy and safety data. Several other collaborative efforts will help to further characterize the therapeutic utility of tenofovir DF in different segments of the HIV-infected population.

5.7. Other Studies

5.7.1. Pediatrics

In addition to study 928 (section 5.2), two phase 1 pediatrics studies are in development. studies 926 and 927 are 48-week open-label pharmacokinetic and safety studies, which target treatment-experienced children with advanced HIV disease.

Conducted at the National Cancer Institute, study 926 will enroll approximately 24 patients and will examine the single and multidose pharmacokinetics of tenofovir DF. In addition, during a 6-day monotherapy period, viral decay dynamics of tenofovir DF will be assessed. All patients will receive one of two doses of tenofovir DF as a component of a new antiretroviral regimen, which has been optimized using data gathered from resistance analyses. Besides evaluation of clinical adverse events and laboratory toxicities, bone metabolism will be measured using bone densitometry and specialized bone biomarkers of resorption and formation.

Study 927 will be conducted at the Necker Hospital in Paris, France, and will enroll approximately 20 patients. The single-dose pharmacokinetics of tenofovir DF will be examined. All patients will receive open-label tenofovir DF as a component of a new antiretroviral regimen, which has been optimized using data gathered from resistance analyses. Studies 926 and 927 are expected to begin enrollment in September 2001 and late 2001, respectively.
5.7.2. **Pharmacokinetics - Renal Impairment**

Since tenofovir is primarily eliminated unchanged by the kidney, a study of the pharmacokinetic disposition of tenofovir DF in patients with varying degrees of renal insufficiency is planned.

5.7.3. **Pharmacokinetics - Hepatic Impairment**

Although tenofovir is primarily eliminated by the kidney, a study of the pharmacokinetic disposition of tenofovir DF in patients with hepatic insufficiency is planned.

5.7.4. **Drug Interactions**

Studies to examine pharmacokinetic drug interactions between tenofovir DF and oral contraceptives, methadone, and enteric-coated didanosine are planned to begin in late 2001. In addition, a study to examine pharmacokinetic drug interactions between tenofovir DF and adefovir dipivoxil 10 mg (in development for the treatment of hepatitis B virus) will be performed.
6. CONCLUSION

Tenofovir DF 300 mg once daily demonstrates statistically significant sustained antiviral activity in HIV-infected patients, including patients with genotypic evidence of nucleoside-resistant virus. To date, there is no evidence of the development clinical resistance to tenofovir DF. In addition, safety data confirm that tenofovir DF is well-tolerated by treatment-experienced HIV-infected patients, for treatment durations as long as 143 weeks. Tenofovir DF offers patients and clinicians a once daily, safe and efficacious agent for use in the treatment of HIV infection.
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8. PRESENTATION SLIDES
Tenofovir Disoproxil Fumarate

NDA 21-356

October 3, 2001

Gilead Sciences, Inc
Foster City, CA

Gilead Consultants

- Harris Genant, M.D.
  Professor of Radiology
  University of California, San Francisco

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  Professor of Medicine
  University of Colorado Health Sciences Center

- Steven L. Teitelbaum, M.D.
  Wilma and Roswell Messing Professor of Pathology & Immunology
  Washington University in St. Louis
Tenofovir Disoproxil Fumarate (TDF)

- Overview of Development Program
  Norbert Bischofberger, Ph.D.

- Clinical Trial Results
  Jay Toole, M.D., Ph.D.

- Phase IV Plans and Concluding Remarks
  Norbert Bischofberger, Ph.D.

Tenofovir Disoproxil Fumarate (TDF)

- Orally bioavailable prodrug of tenofovir (PMPA)
- Nucleotide RTI
- One pill once daily
- Activity against nucleoside resistant virus
Tenofovir DF: Pharmacology and Toxicology

- Efficacious in SIV models
- Long intracellular half-life (15-50 hr)
- Low potential for mitochondrial toxicity (based on in vitro data)
- Not a substrate, inhibitor, or inducer of CYP450 in vitro
- Excreted by kidney
- Main preclinical target organ toxicities:
  - Gastrointestinal - rat and dog
  - Kidney - dog and monkey
  - Bone - rat, dog and monkey

Tenofovir DF: Effects on Bone

- Tenofovir efficacy studies in newborn and juvenile monkeys (UC Davis)
  - Osteomalacia in animals dosed with tenofovir (sc) at 25x human exposure
  - Associated with hypophosphatemia, phosphaturia, ± glucosuria
  - Reversible upon dose reduction or cessation of treatment
  - No radiographic evidence of bone lesions in animals dosed at 8x human exposure for 3 yrs.
Tenofovir DF: Effects on Bone

- 10 month toxicology studies in rats and dogs
  - Marginal to slight reduction in bone mineral density (BMD) (pQCT) in animals dosed with TDF (p.o) at 6-10x human exposure
  - Associated with phosphaturia and calciuria
  - BMD reduction not progressive between 3 and 10 months of treatment
  - No BMD reduction in animals dosed at 2-3x human exposure
- Mechanism
  - Partial blockade of NaPi co-transporters in intestine (decreased PO₄ absorption) and kidney (decreased PO₄ reabsorption)

Tenofovir DF: In Vitro Virology

- Can select in vitro for the K65R mutation in RT
  - 3 to 4-fold reduced susceptibility to tenofovir
- Active in vitro against HIV with
  - ZDV resistance
  - ddl resistance (L74V)
  - ddC resistance (T69D)
  - multinucleoside drug resistance (Q151M)
- Increased activity against HIV with 3TC resistance (M184V)
Tenofovir Susceptibility of Nucleoside-Resistant HIV-1 Clinical Isolates

Virco Antivirogram™ Assay

- M184V: 6.7 (n = 10)
- L74V: 0.7 (n = 5)
- L74V + Y115F + M184V: 0.5 (n = 5)
- T215Y (mean 3.3 TAMs): 3.1 (n = 20)
- Q151M Complex: 1.7 (n = 10)
- K65R: 2.8 (n = 8)
- T69S Insertion: 11.6 (n = 15)

Mean Fold Change From Wild-Type Control

Tenofovir DF: Clinical Studies
Submitted with NDA

- Placebo Controlled Clinical Studies
  - Study 901 Phase I/II (n= 49)
  - Study 902 Phase II (n=185)
  - Study 907 Phase III (n=550)
- Study 908 (n=296)
  - Initiated December 1999 as compassionate access
  - Mean CD4: 36 cells/mL
  - Mean HIV-RNA: 4.9 log_{10} c/mL
- Drug Interaction (Study 914):
  - EVF, IDV, ddl, 3TC, LPV/RTV
- Food Effect (Study 909)
Tenofovir DF: NDA Safety Data Base

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Total</th>
<th>≥ 48 weeks exposure to TDF 300 mg</th>
</tr>
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<tbody>
<tr>
<td>NDA Submission (May 1st)</td>
<td>978</td>
<td>185</td>
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<tr>
<td>NDA Safety update (August 15th)</td>
<td>978</td>
<td>792</td>
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</table>

Tenofovir Disoproxil Fumarate (TDF)

- Overview of Development Program
  Norbert Bischofberger, Ph.D.

- Clinical Trial Results
  Jay Toole, M.D., Ph.D.

- Phase IV Plans and Concluding Remarks
  Norbert Bischofberger, Ph.D.
Clinical Trial Results

- Placebo-controlled Studies

<table>
<thead>
<tr>
<th>Design</th>
<th>Dose (qd)</th>
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<tbody>
<tr>
<td>Study 901</td>
<td>Monotherapy (n=49)</td>
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<tr>
<td></td>
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<tr>
<td>Study 902</td>
<td>Intensification (n=186)</td>
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<td>75, 150 &amp; 300 mg</td>
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<tr>
<td>Study 907</td>
<td>Intensification (n=550)</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
</tr>
</tbody>
</table>

- Renal and Bone Parameters

Study 901

Design

- Randomized, double-blind, placebo-controlled, dose-escalation study of TDF monotherapy
  - HIV RNA ≥ 10,000 copies/mL; CD4 ≥ 200 cells/mm³
  - 4 dose levels (75 mg, 150 mg, 300 mg, 600 mg/day)
- ~10 patients per dose level (8 active, 2 placebo)
- Single dose (day 1) followed by one week washout, then once-daily dosing (days 8 to 35)
- Treatment-naïve and experienced patients were enrolled
## Study 901
### Baseline HIV Characteristics

<table>
<thead>
<tr>
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<th>Active (n=38)</th>
<th>Placebo (n=11)</th>
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<tbody>
<tr>
<td>Mean CD4 (cells/mm³)</td>
<td>391</td>
<td>346</td>
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<tr>
<td>Mean HIV RNA (copies/mL)</td>
<td>85,351</td>
<td>115,593</td>
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<tr>
<td>Prior ART use</td>
<td>68%</td>
<td>36%</td>
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## Study 901
### HIV RNA

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=9)</th>
<th>75 mg (n=10)</th>
<th>150 mg (n=8)</th>
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<th>600 mg (n=8)</th>
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<td>Day 35</td>
<td>0.03</td>
<td>-0.33*</td>
<td>-0.51*</td>
<td>-1.20*</td>
<td>-0.84*</td>
</tr>
<tr>
<td>Log₁₀ c/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p-values < 0.003
**Study 901**

**Mean Change from Baseline in HIV-1 RNA Intent to Treat**

![Graph showing mean change from baseline in HIV-1 RNA over days of study.](image)

- **Placebo**: 11 9 8 9 8 9 9 8
- **TDF 75 mg**: 12 12 12 12 11 10 10 11
- **TDF 150 mg**: 8 7 8 8 9 9 9 8
- **TDF 300 mg**: 8 8 8 8 7 8 7 7
- **TDF 600 mg**: 10 9 8 9 9 8 7 4

**DAYS OF STUDY**

**Study 902**

**Design**

- Randomized, double-blind placebo-controlled study of TDF added to existing antiretroviral regimen
- **Entry criteria:**
  - Stable ART ≥ 8 weeks prior to entry consisting of ≤ 4 concomitant antiretroviral agents
  - HIV RNA ≥ 400 - 100,000 copies/mL
- **Primary Efficacy Endpoint**
  - Time-weighted average change from baseline in HIV RNA (log₁₀ c/mL) at week 24 (DAVG₂₄)
Study 902
Design

- Double-blind
- Open Label

<table>
<thead>
<tr>
<th>24 wks</th>
<th>48 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable ART ≥ 8 weeks randomized 2:2:2:1</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

Study 902
HIV Baseline Characteristics (n=186)

- Mean CD4 (cells/mm³) 374
- Mean HIV RNA (copies/mL) 16,583
- Mean prior ART (years) 4.6
- Baseline resistance
  - NNRTI 32%
  - PI 57%
  - NRTI 94%
<table>
<thead>
<tr>
<th>Study 902</th>
<th>Patient Disposition (0-24 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TDF</strong></td>
<td>Placebo</td>
</tr>
<tr>
<td>Patients who received drug</td>
<td>28</td>
</tr>
<tr>
<td>Patients discontinued (%)</td>
<td>7 (25%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Lack of virologic response</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study 902</th>
<th>Patient Disposition (0-48 Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TDF</strong></td>
<td>75 mg</td>
</tr>
<tr>
<td>Patients who received drug</td>
<td>53</td>
</tr>
<tr>
<td>Patients discontinued (%)</td>
<td>14 (26%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Lack of virologic response</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>
### Study 902

#### Grade 3/4 Adverse Events (0-24 Weeks)*

<table>
<thead>
<tr>
<th>Patients (%) with Events</th>
<th>TDF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75 mg (n=53)</td>
<td>150 mg (n=51)</td>
</tr>
<tr>
<td>Depression</td>
<td>0 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Fever</td>
<td>1 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

Note: >1% in either TDF or placebo

### Study 902

#### Grade 3/4 Laboratory Abnormalities (0 - 24 Weeks)*

<table>
<thead>
<tr>
<th>Patients (%) with Abnormality</th>
<th>Placebo (n=28)</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75 mg (n=53)</td>
<td>150 mg (n=51)</td>
</tr>
<tr>
<td>Triglyceride elevation</td>
<td>4 (14%)</td>
<td>9 (17%)</td>
</tr>
<tr>
<td>Creatine kinase elevation</td>
<td>4 (14%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>AST elevation</td>
<td>1 (4%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (4%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>1 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Lipase elevation</td>
<td>1 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Amylase elevation</td>
<td>1 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>0</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Glucosuria</td>
<td>0</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Bilirubin elevation</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: >1% in either TDF or placebo
### Study 902

**Primary Efficacy Endpoint**

Mean DAVG$_{24}$ ($\log_{10}$ c/mL)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TDF 75 mg</th>
<th>TDF 150 mg</th>
<th>TDF 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent to Treat</td>
<td>+0.02</td>
<td>-0.26</td>
<td>-0.34</td>
<td>-0.58*</td>
</tr>
<tr>
<td>As Treated</td>
<td>+0.16</td>
<td>-0.16</td>
<td>-0.32*</td>
<td>-0.52*</td>
</tr>
</tbody>
</table>

*p-value < 0.001

---

**Study 902**

**Mean Change from Baseline in HIV-1 RNA**

Intent to Treat

![Graph showing mean change from baseline in HIV-1 RNA over weeks for different dosage groups.](image-url)

- Placebo
- 75 mg
- 150 mg
- 300 mg

*Weeks:* 0, 12, 24, 36, 48

*Participants:* 53, 48, 49, 93, 49, 44, 49, 48, 48, 48, 42

*Note:* Detailed data points and statistical significance not provided in this summary.
### Study 902

#### CD4 Count

<table>
<thead>
<tr>
<th></th>
<th>TDF Placebo (n=28)</th>
<th>TDF 75mg (n=53)</th>
<th>TDF 150mg (n=51)</th>
<th>TDF 300mg (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 24</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>-14</td>
</tr>
<tr>
<td>Week 48</td>
<td>N/A</td>
<td>10</td>
<td>20</td>
<td>11</td>
</tr>
</tbody>
</table>

### Study 902

#### Virology

Response by Baseline Resistance Mutations

<table>
<thead>
<tr>
<th>Baseline Mutations</th>
<th>Mean DAVG_{24} (log_{10} c/mL)</th>
<th>Placebo (n=28)</th>
<th>TDF 300mg (n=54)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M184V</td>
<td>+0.08 (16)</td>
<td>-0.64 (21)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ZDV- R</td>
<td>+0.17 (20)</td>
<td>-0.52 (40)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>NNRTI - R</td>
<td>+0.25 (8)</td>
<td>-0.46 (17)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>PI - R</td>
<td>+0.21 (18)</td>
<td>-0.61 (33)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Study 907

Design

- Randomized, double-blind, placebo-controlled study of TDF added to existing antiretroviral regimen
- Entry criteria:
  - Stable ART ≥ 8 weeks prior to entry consisting of ≤ 4 concomitant antiretroviral agent
  - HIV RNA ≥ 400 - 10,000 copies/mL
- Primary efficacy endpoint
  - Time-weighted average change from baseline in HIV-1 RNA (log_{10} c/mL) at week 24 (DAVG_{24})
### Study 907
#### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=182)</th>
<th>TDF (n=368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>160/22</td>
<td>309/59</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>65%</td>
<td>71%</td>
</tr>
<tr>
<td>African-American</td>
<td>19%</td>
<td>16%</td>
</tr>
<tr>
<td>Other</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Antiretroviral Regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease-containing</td>
<td>58%</td>
<td>53%</td>
</tr>
<tr>
<td>NNRTI-containing</td>
<td>36%</td>
<td>43%</td>
</tr>
</tbody>
</table>

### Study 907
#### HIV Characteristics

- **Baseline Means**
  - HIV RNA (copies/mL) 4365 4502
  - CD4 count (cells/mm³) 338 335
  - ART use (years) 5.3 5.5
Study 907
Virology Substudy

Baseline Genotyping (n=253)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary resistance mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- NNRTI</td>
<td>52%</td>
<td>46%</td>
</tr>
<tr>
<td>- PI</td>
<td>62%</td>
<td>57%</td>
</tr>
<tr>
<td>- NRTI</td>
<td>94%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Study 907
Patient Disposition
0-24 weeks

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who received drug</td>
<td>182</td>
<td>368</td>
</tr>
<tr>
<td>Patients discontinued (%)</td>
<td>11 (6%)</td>
<td>23 (6%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>5 (3%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Lack of virologic response</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>2 (1%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1%)</td>
<td>5 (1%)</td>
</tr>
</tbody>
</table>
### Study 907
#### Grade 3/4 Adverse Events
(0-24 Weeks)*

<table>
<thead>
<tr>
<th>Patients (%) with events</th>
<th>Placebo (n=182)</th>
<th>TDF (n=368)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 (13%)</td>
<td>51 (14%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (2%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>Pain</td>
<td>2 (1%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2 (1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Peripheral Neuritis</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorder</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*≥ 1% in either group

### Study 907
#### Grade 3/4 Laboratory Abnormalities
(0-24 Weeks)*

<table>
<thead>
<tr>
<th>Patients (%) with abnormality</th>
<th>Placebo (n=182)</th>
<th>TDF (n=368)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>68 (37%)</td>
<td>89 (25%)</td>
</tr>
<tr>
<td>Triglyceride elevation</td>
<td>24 (13%)</td>
<td>30 (8%)</td>
</tr>
<tr>
<td>Creatine kinase elevation</td>
<td>26 (15%)</td>
<td>24 (7%)</td>
</tr>
<tr>
<td>Amylase elevation</td>
<td>13 (7%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>Glucosuria</td>
<td>6 (3%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>AST elevation</td>
<td>5 (3%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>8 (4%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>3 (2%)</td>
<td>8 (2%)</td>
</tr>
</tbody>
</table>

*≥ 1% in either group
Study 907
Primary Efficacy Endpoint
Intent to Treat

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=182)</th>
<th>TDF (n=368)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean DAVG_{24} (log_{10} c/mL)</td>
<td>-0.03</td>
<td>-0.61</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Study 907
Mean Change from Baseline HIV-1 RNA
Intent to Treat

![Graph showing mean change from baseline HIV-1 RNA levels over weeks on study.](image)
### Study 907

#### Subgroup Analyses

<table>
<thead>
<tr>
<th></th>
<th>Mean $\text{DAVG}_{24}$</th>
<th>Placebo</th>
<th>TDF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt; 5,000</td>
<td>0.03</td>
<td>-0.59</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>≥ 5,000</td>
<td>-0.22</td>
<td>-0.67</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>CD4 &lt; 200</td>
<td>0.05</td>
<td>-0.39</td>
<td>0.0007</td>
<td></td>
</tr>
<tr>
<td>≥ 200</td>
<td>-0.04</td>
<td>-0.64</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-0.02</td>
<td>-0.61</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>-0.08</td>
<td>-0.66</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>-0.02</td>
<td>-0.60</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Non-caucasian</td>
<td>-0.05</td>
<td>-0.65</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

#### Secondary Efficacy Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TDF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA ≤ 400 copies/mL</td>
<td>13%</td>
<td>45%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HIV RNA ≤ 50 copies/mL</td>
<td>1%</td>
<td>22%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$\text{DAVG}_{24}$ CD4 (cells/mm³)</td>
<td>-11</td>
<td>+13</td>
<td>0.0008</td>
</tr>
</tbody>
</table>
### Study 907

**Virology Substudy**

Response by Baseline Resistance Mutations

As Treated

<table>
<thead>
<tr>
<th>Baseline Mutations</th>
<th>Placebo Mean ( \text{DAVG}_{24} ) (log₁₀ c/mL)</th>
<th>TDF Mean ( \text{DAVG}_{24} ) (log₁₀ c/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M184V</td>
<td>-0.04 (54)</td>
<td>-0.67 (117)*</td>
</tr>
<tr>
<td>ZDV- R</td>
<td>+0.03 (61)</td>
<td>-0.47 (113)*</td>
</tr>
<tr>
<td>NNRTI - R</td>
<td>+0.03 (44)</td>
<td>-0.48 (76)*</td>
</tr>
<tr>
<td>PI - R</td>
<td>+0.01 (52)</td>
<td>-0.55 (96)*</td>
</tr>
</tbody>
</table>

* p-values <0.0001

---

### Study 907

**Virology Substudy**

Development of Resistance Mutations

(0-24 weeks)

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Placebo (n=91)</th>
<th>TDF (n=183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI-related</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>PI-related</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Nucleoside-related</td>
<td>22%</td>
<td>15%</td>
</tr>
<tr>
<td>- K65R</td>
<td>0</td>
<td>3%</td>
</tr>
</tbody>
</table>
Study 902 and 907
Renal and Bone Parameters
Integrated Safety Analysis

- Includes all patients who received 300 mg (n=687)
  - As randomized (n=422)
  - Following placebo cross-over (n=191)
  - Following 48 weeks of either 75 or 150 mg (n=74)

Studies 902 and 907
Integrated Safety Analysis*

- Number of patients: 687
  - n ≥ 48 weeks exposure: 480
  - n ≥ 72 weeks exposure: 156
- Mean (weeks): 58
- Maximum (weeks): 143

*Through June 1, 2001
### Study 907

**Serum Creatinine**

**Maximum Toxicity Grade**

(0-24 weeks)

<table>
<thead>
<tr>
<th>Grade (mg/dL)</th>
<th>Placebo (n=182)</th>
<th>TDF (n=368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (≥ 0.5 from baseline)</td>
<td>2 (1%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>2 (2.1 - 3.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 (3.1 - 6.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4 (&gt; 6.0)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Studies 902 & 907

**Serum Creatinine**

**Maximum Toxicity Grade**

(0-143 weeks)

<table>
<thead>
<tr>
<th>Grade (mg/dL)</th>
<th>TDF (n=687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (≥ 0.5 from baseline)</td>
<td>32 (5%)</td>
</tr>
<tr>
<td>2 (2.1 - 3.0)</td>
<td>0</td>
</tr>
<tr>
<td>3 (3.1 - 6.0)</td>
<td>0</td>
</tr>
<tr>
<td>4 (&gt; 6.0)</td>
<td>0</td>
</tr>
</tbody>
</table>
### Studies 902 & 907

**Creatinine Elevations are Transient**

![Bar graph showing consecutive visits with grade 1 creatinine levels.]

### Study 907

**Serum Phosphorus**

**Maximum Toxicity Grade**

(0-24 weeks)

<table>
<thead>
<tr>
<th>Grade (mg/dL)</th>
<th>Placebo (n=182)</th>
<th>TDF (n=368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (2.0-2.2)</td>
<td>10 (5%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>2 (1.5-1.9)</td>
<td>4 (2%)</td>
<td>23 (6%)</td>
</tr>
<tr>
<td>3 (1.0-1.4)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>4 (&lt;1.0)</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>
Studies 902 & 907

Serum Phosphorus
Maximum Toxicity Grade
(0-143 weeks)

<table>
<thead>
<tr>
<th>Grade (mg/dL)</th>
<th>TDF (n=687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (2.0-2.2)</td>
<td>51 (7%)</td>
</tr>
<tr>
<td>2 (1.5-1.9)</td>
<td>58 (8%)</td>
</tr>
<tr>
<td>3 (1.0-1.4)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>4 (&lt;1.0)</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

Studies 902 & 907

Hypophosphatemia is Transient

Consecutive visits serum phosphate < 2.0 mg/dL
### Studies 902 & 907

#### Bone Fracture Rate

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Total Exposure (patient-yrs)</th>
<th>No. Fractures</th>
<th>Fracture Rate* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (0-24 wks)</td>
<td>210</td>
<td>99</td>
<td>3</td>
<td>3.0 (0.6-8.9)</td>
</tr>
<tr>
<td>TDF (0-143 wks)</td>
<td>687</td>
<td>778</td>
<td>14</td>
<td>1.8 (0.9-3.0)</td>
</tr>
</tbody>
</table>

*Per 100 patient-years

### Studies 902 and 907

#### Bone Fracture Summary

- External review of radiographs (H. Genant, M.D., UCSF)
- No vertebral compression fractures
  - Fractures result of high-impact trauma
  - Normal healing observed while TDF continued
- TDF event rate is similar to placebo
  - Rate has not increased with longer exposure
Tenofovir DF: Safety Summary

- The safety of TDF 300 mg is similar to placebo through 24 weeks
- The safety of TDF shows no significant change with extended dosing

Tenofovir DF: Efficacy Summary

- TDF 300 mg monotherapy resulted in \(-1.2 \log_{10} \text{ c/mL change from baseline}\) (901)
- TDF added to background regimens produced a significant reduction from baseline in HIV RNA of approximately \(0.6 \log_{10} \text{ c/mL}\) in treatment-experienced patients (902 & 907)
  - durable through 48 weeks
Efficacy Summary
(Continued)

• TDF produced a significant increase in the percentage of patients with (907)
  – HIV RNA ≤ 400 copies/mL
  – HIV RNA ≤ 50 copies/mL
• Genotypic analyses demonstrate (902 & 907)
  – activity in patients with common HIV resistance mutations
  – low incidence of TDF resistance mutation development

Tenofovir DF: Clinical Conclusions

• TDF is safe and well-tolerated
• TDF provides durable antiviral suppression
• TDF has a favorable resistance profile
Tenofovir DF: Indication

Tenofovir DF is indicated in combination with other antiretroviral agents for the treatment of HIV infection in adults.

Tenofovir Disoproxil Fumarate (TDF)

- Overview of Development Program
  Norbert Bischofberger, Ph.D.

- Clinical Trial Results
  Jay Toole, M.D., Ph.D.

- Phase IV Plans and Concluding Remarks
  Norbert Bischofberger, Ph.D.
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- Phase IV Plans and Concluding Remarks
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IIIb/IV Ongoing & Planned Studies

- Long term safety follow-up:
  - Study 910: Open label rollover study from 902 and 907 (n=575)
  - Study 903: Confirmatory study (n = 601)

- Pediatric development program:
  - Studies 926, 927: Phase II/III
  - Study 928: Phase III

- Expanded Access Programs:
  - Studies 950-955: US, Europe, Canada, Australia
    Enrollment (September 2001): 5000
Study 910

• Rollover protocol from studies 901, 902 and 907 (n=575)
• Continuing to evaluate patients through December 2002
  - Safety
  - Virology
  - BMD substudy (n = 87)
• Allows > 4 years of follow up for patients treated with TDF 300 mg

Confirmatory Study 903

• Design
  - Antiretroviral naïve patients
  - Randomization:
    1:1 EFV + 3TC + D4T
    EFV + 3TC + TDF
  - Blinded
• Enrollment completed 1/01; n = 601
• Bone evaluations in all patients:
  - BMD (DXA)
  - Bone biomarker (osteocalcin, bALP, N&C-teleopeptide, VitD, PTH)
• Endpoints
  - Efficacy: proportion of patients with HIV-RNA < 400 c/mL at week 48
  - Safety
• Duration of blinded study extended to 96 weeks
Study 903
Baseline Characteristics

- Female 26%
- Mean Age 35 years
- HIV-Related
  - Median HIV-RNA: $4.89 \log_{10}$ copies/mL
    Range: 2.6 - 6.49
  - Median CD4 Count: 262 cells/mL
    Range: 3 - 1071
  - % Symptomatic: 38%

Pediatric Development

- Pediatric development deferred pending safety evaluation in adults
- Pediatric formulation in development, available Q1 2002
- Phase I/II studies:
  - Study 926: Single/multiple dose PK
    n=10 (France); initiated 9/01
  - Study 927: 48 week, safety, efficacy
    n= (NCI); initiated 10/01
- Phase III study:
  - 48 week placebo controlled study of TDF added to optimized background regimens
  - 2nd confirmatory study
Tenofovir DF: Conclusions

- Evidence for safety and efficacy from controlled clinical studies (901, 902, 907)
- Evidence of longer term safety (renal, bone) from safety update
- Long term safety and efficacy studies (903, 910) in progress
- Pediatric development and additional supportive studies initiated or planned
To: Therapeutic Specialists
cc: Region Directors, NAMs, Clifford Samuel, Sheryl Meredith, Shay Weisbrich, Jim Meyers, Kristin Bennett, Chris Garabedian
From: Amiel Balagtas, John Windt, Kelly Seither, Linda Cherry
Date: January 27, 2003
Re: Viread® HIV/HBV Co-infection Articles

Enclosed for your reference and training only is a copy of two recently published articles describing the use of VIREAD in HIV/HBV co-infected patients. The first, authored by Mark Naeye from the Chelsea and Westminster Hospital in London and published in the January 3, 2003 issue of the Journal AIDS, is titled "An open-label study of tenofovir in HIV-1 and Hepatitis B co-infected individuals." The second article, titled "Tenofovir Disoproxil Fumarate in Patients with HIV and lamivudine-resistant Hepatitis B Virus," was authored by Yves Benhamou and published in the correspondence section of the January 9, 2003 edition of the New England Journal of Medicine.

"An open-label study of tenofovir in HIV-1 and Hepatitis B co-infected individuals," AIDS
Please note that the dose of VIREAD is listed as 245 mg. This is due to the fact that the labeled dose of VIREAD in Europe is based on the active component of the drug (tenofovir disoproxil) and does not include the weight of the inert-salt component (fumarate).

Please note that VIREAD is not approved for the treatment of hepatitis B. No data on activity against hepatitis B are included in the US prescribing information for VIREAD.

Baseline Characteristics
- 20 HIV/HBV (HBe antigen positive) co-infected male patients had VIREAD added to their existing therapy
- 15 of 20 patients were 3TC experienced (median 13 weeks); 11 of whom had 3TC-associated resistance mutations (10 YMDD, 1 YIDD)

Results
Through 24 weeks:
- Median 4 log₁₀ decline in HBV DNA (no difference between 3TC-naïve or experienced patients, although the initial rate of decline of HBV DNA was more rapid in subjects with 3TC-resistance mutations, p=0.046)
- Median decrease in ALT from 96 to 42 IU/ml (46% of patients normalized ALT)
- Two patients seroconverted to HBe-antibody positive (five patients through week 52)
- Trend toward an improved CD4 cell count and CD4 percentage
- No patients experienced drug-related toxicities
**Discussion**

- Dr. Nelson states that the study demonstrates that VIREAD is effective against HBV in HIV-1 infected individuals who have been previously exposed to 3TC.

- Adenosine diphosphoribose (ADV) is also mentioned in this section. The author references HIV/HBV coinfection data (Benhamou, Lancet 2001) and mentions that at 10 mg, ADV demonstrates no activity against HIV-1, but caused increases in ALT and the development of diabetes was seen. It is important to note that the increases in ALT were transient and all patients continued therapy with ADV and that the one patient who developed diabetes had a family history of the disease.

"Tenofovir Disoproxil Fumarate in Patients with HIV and Lamivudine-Resistant Hepatitis B Virus," *The New England Journal of Medicine*

**Baseline Characteristics**

- 12 HIV/HBV co-infected men had VIREAD added to their existing therapy which included lamivudine 150 mg bid.

- All patients were seropositive for HBV DNA for a median of 30 months prior to the addition of VIREAD.

- Ten patients had documented HBV resistance mutations.

**Results**

Through 24 weeks:

- Mean 3.83 log₁₀ decrease in HBV DNA (p=0.003).

- None of the patients had loss of hepatitis B e antigen or seroconversion to anti-hepatitis B e.

- CD4 count increased by 77 cells/mm³ (p=0.016).

- Levels of HIV RNA and serum ALT did not change significantly.

- One patient with polycystic kidney disease discontinued at week 22 due to an increase in serum creatinine (which returned to pretreatment levels after discontinuing VIREAD).

**Conclusion**

- Preliminary results suggest that VIREAD may be effective for the treatment of lamivudine-resistant HBV in HIV co-infected patients.

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**THIS MATERIAL IS PROVIDED FOR YOUR INFORMATION ONLY AND SHOULD NOT BE DISTRIBUTED TO CUSTOMERS. ADDITIONALLY, PLEASE DO NOT USE THESE ARTICLES TO INITIATE DISCUSSIONS WITH YOUR CUSTOMERS.**
An open-label study of tenofovir in HIV-1 and Hepatitis B virus co-infected individuals

M. Nelson, S. Portsmouth, J. Stebbing, M. Atkins, A. Barr, G. Matthews, D. Pillay\textsuperscript{a}, M. Fisher\textsuperscript{b}, M. Bower and B. Gazzard

**Background:** Tenofovir is a novel nucleotide analogue recommended for use in HIV-1 infected treatment-experienced patients. Recent data suggest an effect on Hepatitis B virus (HBV) replication. We therefore investigated the use of tenofovir in HIV-1 and HBV co-infected individuals.

**Methods:** Twenty HIV-1/HBV co-infected patients with a median of 108 weeks lamivudine experience (range, 0–270 weeks) received tenofovir 245 mg daily in addition to or as part of their combination antiretroviral therapy. Their immunologic parameters and HIV-1 RNA and HBV DNA viral loads were followed over a period of 52 weeks. In addition, their HBV DNA polymerase was sequenced at baseline to measure the frequency of YMDD mutations that are associated with lamivudine resistance.

**Findings:** A significant decrease in HBV DNA viral load (4 × log\textsubscript{10}) and alanine aminotransferase levels was observed. There were no significant overall differences between the lamivudine-experienced (n = 15) and -naive (n = 5) individuals and tenofovir was well tolerated. Five patients (25%) underwent HBe antigen seroconversion during the study period. Out of the 15 lamivudine-experienced individuals, 10 had YMDD mutations and one had YIDD mutations in HBV DNA.

**Interpretation:** These results indicate that 52 weeks of tenofovir in addition to antiretroviral therapy is active against HBV, and it appears to overcome lamivudine resistance.

_AIDS_ 2003, 17:F7–F10

**Keywords:** lamivudine, tenofovir, hepatitis B, HIV-1, antiretroviral therapy, resistance mutation

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**Introduction**

HIV-1 infection is commonly complicated by co-infection with Hepatitis B virus (HBV) [1]. Chronic hepatitis B is a widespread disease affecting more than 350 million people worldwide — approximately 5% of the world’s population [2,3]. The two therapies currently licensed for hepatitis B are interferon-α and lamivudine (3TC) [4]. The cytokine interferon-α given subcutaneously results in variable and often unsatisfactory response rates with significant adverse effects [5]. The nucleoside analogue reverse transcriptase inhibitor (NRTI) 3TC is well tolerated and inhibits HBV replication in more than 80% of patients with or without HIV-
1 co-infection [6-8]. Emergence of HBV resistance to 3TC occurs in 50% and 90% of HIV-1/HBV co-infected patients after 2 and 4 years of therapy respectively [9]. This is conferred by a mutation in the HBV DNA polymerase gene which entails a substitution of the methionine residue at codon 550 in the YYMD (Tyr-Met-Asp-Asp) motif by either valine or isoleucine [10,11]. The clinical consequences on the course of HBV infection of 3TC resistance in HIV-infected individuals are currently unknown [12].

Tenofovir R-9-(2-phosphonyl-methoxypropyl)adenine is an acyclic nucleotide reverse transcriptase inhibitor [13]. It has a safety profile comparable to placebo and a randomized study has shown dose-related, durable reductions in HIV-1 RNA viral load with activity against NRTI-resistant virus [14].

The in vitro activity of tenofovir against HBV was first demonstrated in 1990 [15] and recent subgroup analyses of HIV-1/HBV co-infected individuals treated with tenofovir showed a reduction in HBV DNA viral load. Patients included in this were 3TC-experienced and harboured YYMD mutations [16]. We therefore wished to study the effects of tenofovir in HIV-1/HBV co-infected patients.

Methods

From August 2001 to January 2002, 20 HIV-1/HBV co-infected subjects at The Chelsea and Westminster Hospital and Royal Sussex County Hospital, UK were treated with standard antiretroviral therapy as per unit protocol with the addition of 245 mg of tenofovir orally once daily. All were HBe antigen positive. These patients were treated as part of salvage protocols or because of increased HBV DNA despite prolonged use of 3TC.

Patients were followed up in routine HIV clinics at baseline, 4, 12, 24 weeks and then 12 weekly. Hepatitis B serology was performed along with quantitative HBV DNA levels with a baseline detection limit of <1 x 10^4 genome equivalents (GEq)/ml [17]. The presence of YYMD mutations was established in baseline blood samples by sequencing of the HBV DNA polymerase [18]. Total lymphocyte and subset analysis was performed using whole blood stained with murine anti-human monoclonal antibodies to CD4, CD8, CD16/56 and CD19 (Tetramax, Beckman Coulter, High Wycombe, UK) and were evaluated on an Epics XL-MCL (Beckman Coulter) flow cytometer. Viral loads in patient plasma was measured using the Quantiplex HIV RNA 3.0 (Chiron bDNA) assay with a lower limit of detection of 50 HIV-1 copies/ml (Chiron Diagnostics, Halstead, UK). These parameters were measured at most clinic visits. Alanine aminotransferase (ALT) and albumin levels were recorded. All individuals gave written informed consent and the study received ethical approval in accordance with the Helsinki declaration.

Results

All 20 patients were homosexual males and their median age was 43 years (range, 22-52 years). Fifteen out of the 20 patients were 3TC experienced with a median exposure of 138 weeks (range, 8-270 weeks). The median HBV DNA viral load at baseline was 181 500 000 (interquartile range, 47 375 000–755 000 000) GEq/ml. Out of these 15 3TC exposed patients, 11 had mutations at baseline conferring 3TC escape (10 with YMDD and one with YIDD).

Concurrent antiretroviral regimens in addition to tenofovir consisted of: (i) a non-nucleoside reverse transcriptase inhibitor (NNRTI) and two NRTI in nine patients (45%); (ii) three NRTI in three patients (15%); (iii) two NRTI and a boosted protease inhibitor (PI) in two patients (10%); (iv) two PI and two NRTI in two patients (10%); (v) an NNRTI and one NRTI in two patients (10%); (vi) two PI and one NRTI in one patient (5%); and (vii) one PI and three NRTI in the remaining patient (5%). Subgroup analyses contained too few patients to draw useful comparisons although it appeared that there were no significant differences (data not shown).

We observed a median 4 log_{10} reduction in HBV DNA viral load in the first 24 weeks and a median decrease in ALT from 96 to 43 IU/ml during this time (46% normalized their ALT during the trial). Serum albumin showed a small non-significant increase (Fig. 1). The median in HBV DNA viral load decreased from 126 272 450 GEq/ml to 328 692 during the first 24 weeks. Table 1 demonstrates the percentage of patients with an undetectable HBV load at each time point and the number of patients in the trial who reached this time.

There was a trend towards an improved CD4 cell count and CD4 cell percentage. There were no significant changes in CD8 cell count and the median HIV-1 viral load remained below the limit of detection (Fig. 2). Similarly, CD16/CD56 and CD19 counts remained unchanged.

At 24 weeks, two patients had seroconverted and by 52 weeks, five patients (25%) had seroconverted to HBs-antibody positivity. Three of these five individuals harboured 3TC resistant mutations. No patients experienced any drug-related toxicities or unwanted effects.
Tenofovir in HIV-1/HBV co-infection Nelson et al.

Fig. 1. Changes in hepatic parameters with time. (a) Log_{10} HBV DNA viral load in the 20 patients (the lower limit of detection is 10^4 Geq/ml); (b) ALT; and (c) albumin levels. The medians and interquartile ranges are shown.

Table 1. Cumulative number of patients with an undetectable HBV DNA viral load during the study and the number of individuals reaching each time point.

<table>
<thead>
<tr>
<th>Time on therapy (weeks)</th>
<th>4 weeks</th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>36 weeks</th>
<th>52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number on study</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Cumulative number</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>10</td>
<td>13</td>
</tr>
</tbody>
</table>

and one patient elected to stop therapy as he wished to discontinue antiretroviral treatment. Serum electrolytes and creatinine remained stable.

The rate of decrease in HBV DNA viral load demonstrated a more rapid initial decline in those individuals who harboured 3TC-resistant mutations compared with those who did not (P = 0.046; one-sided test of variance/central limit theorem; Fig. 3).

Discussion

This study demonstrates that tenofovir is effective against HBV in HIV-1 infected individuals who have been previously exposed to 3TC and suggests that tenofovir may be used to overcome 3TC resistance.

Anti-HBV efficacy is important in co-infected patients as HIV-1 induced immunosuppression leads to increased HBV replication [12]. We also observed a statistically significant more rapid decline in the slope of HBV DNA decay between those individuals who harboured YMDD mutations and those who did not.

Historically, the development of anti-HIV-1 therapy led to early trials of monotherapy. This resulted in the
accumulation of drug resistant mutations and subsequent treatment failure. Similarly, 3TC monotherapy for HBV infection leads to the rapid development of mutants that no longer respond to treatment [19]. This in turn has implications for the clinical outcome of chronic infection including cirrhosis and hepatocellular carcinoma [20]. The use of tenofovir and 3TC as part of a highly active antiretroviral therapy regimen may have superior potency and durability against both HIV-1 and HBV infection.

Tenofovir, at a dose of 10 mg daily, is active against 3TC-resistant HBV in HIV-1/HBV co-infected individuals [12]. At this dose, no activity against HIV-1 was observed although increased ALT and the development of diabetes were seen. At an HIV-1 treatment dose of either 60 mg or 120 mg daily, nephrotoxicity has been observed in 33% and 42% of patients, respectively [21]. Tenofovir at an HIV-1 treatment dose is active against HBV with no renal toxicity.

The loss of HBeAg in two patients in a relatively short time scale of 24 weeks and in five patients at 1 year is encouraging and should be studied in a larger cohort of patients including HIV-negative HBV-infected individuals. In the largest study using adefovir [12], two patients out of 35 underwent HBe antigen seroconversion. However, the safety profile of tenofovir is comparable to that of placebo [14] and we observed no adverse effects. Tenofovir increases the therapeutic options for HIV-1 and HBV co-infection.

Acknowledgements

Sponsorship: Supported by Gilead UK, Cambridge.

References

surgical debridement. Despite all these measures, the patient did not have a response. The mortality rate associated with streptococcal toxic shock syndrome remains high, and new treatments are clearly needed.

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TO THE EDITOR: Mutations in the YMDD (tyrosine, methionine, aspartate, aspartate) motif of the DNA polymerase resulting in phenotypic hepatitis B virus (HBV) resistance to lamivudine monotherapy have been observed after two years in 50 percent of patients coinfected with the human immunodeficiency virus (HIV). Adefovir dipivoxil has been shown to be effective for lamivudine-resistant HBV infection in HIV-coinfected patients. Tenofovir disoproxil fumarate, a nucleotide reverse-transcriptase inhibitor, is active against HIV and has in vitro activity against wild-type and lamivudine-resistant HBV.

We examined the efficacy and safety of tenofovir disoproxil fumarate, at a dose of 300 mg given once daily, in HIV-coinfected patients with lamivudine-resistant HBV infection. The study was approved by our institutional review board, and all the patients provided written, informed consent. Paired t-tests were used to assess changes from base line. Twelve men (mean ±SE age, 44.1±3.6 years) who were coinfected with HIV and HBV and whose regimen included lamivudine (150 mg given twice daily) had tenofovir disoproxil fumarate added to their regimen. They were evaluated at 4, 8, 12, and 24 weeks. The patients were serum-positive for HBV DNA for a median of 30 months (range, 10 to 34) before the administration of tenofovir disoproxil fumarate was initiated. Ten patients had documented HBV polymerase mutations (rtM204V/rtL180M in eight and rtM204V/rtL180M in two). Serum HBV DNA and plasma HIV RNA levels were assessed by the polymerase chain reaction (Roche Amplicor; sensitivity, 2.6 and 2.3 log_{10} copies per milliliter, respectively). From base line to week 24, serum HBV DNA levels decreased in all the patients (P=0.003) (Fig. 1). None of the patients had loss of hepatitis B e antigen or seroconversion to anti–hepatitis B e. Sequencing at week 24, performed in four patients, revealed base-line mutations but no new mutations in domain B or C of the polymerase. The CD4 cell count at base line (mean, 440±66 cells per cubic millimeter) had increased by 77±27 cells per cubic millimeter at week 24 (P=0.016). The levels of HIV RNA and serum alanine aminotransferase did not change significantly during the study. The tenofovir disoproxil fumarate was generally well tolerated. One patient, who had poly cystic kidney disease, withdrew at week 12 because of an increase in his serum creatinine level (from 2.8 mg per deciliter to a maximum of 4.5 mg per deciliter, without a change in the serum levels of potassium, phosphorus, or bicarbonate). After the administration of tenofovir disoproxil fumarate was discontinued, serum creatinine and serum HBV DNA returned to their pretreatment levels.

These preliminary, 24-week data suggest that 300 mg of tenofovir disoproxil fumarate given once daily may be effective for the treatment of lamivudine-resistant HBV infection in HIV coinfected patients.
Hepatitis C Virus, Human Herpesvirus 8, and the Development of Plasma-Cell Leukemia

TO THE EDITOR: The role of hepatitis C virus (HCV) and human herpesvirus 8 (HHV-8), two B-cell-tropic viruses, in B-cell proliferation is illustrated by the following unusual case of plasma-cell leukemia. In 1995, a 32-year-old man with a history of hepatitis A virus and HCV infection but who tested negative for hepatitis B virus and human immunodeficiency virus was admitted to the hospital with septic shock, bilateral pneumonia, and hepatosplenomegaly. The hemoglobin level was 8.9 g per deciliter; the white-cell count was 26,6x10^9 per liter with 50 percent plasmablasts (Fig. 1A), 41 percent neutrophils, 7 percent lymphocytes, and 2 percent monocytes; the platelet count was 99x10^9 per liter. The bone marrow contained 47 percent plasmablasts. The protein level was 57 g per liter, with 15.5 g per liter of gamma globulins and a monoclonal IgG kappa in serum and urine. Antibiotics and chemotherapy (cytosine arabinoside, dexamethasone, vincristine, and cyclophosphamide) were administered, but the patient, who had severe thrombocytopenia, died of a brain hemorrhage on day 15.

All plasmablasts were CD38+CD138+CD56−CD28− and positive for IgG kappa. They were also CD19−CD45++, a phenotype usually found in reactive plasma-cell proliferations. However, cytogenetic and fluorescence in situ hybridization analysis confirmed monoclonality and revealed an isolated t(9;14)(p13;q32) translocation, which fused the PAX-5 and IgH genes. This translocation occurs in cases of lymphoplasmacytoid lymphoma, one third of which are associated with HCV.1,2 and was reported in tumor cells of an HCV-positive patient with primary-effusion lymphoma, a condition associated with HHV-8.3

Retrospective studies were consistent with an HCV-driven process leading to plasma-cell leukemia. Immunoblotting showed that the monoclonal IgG kappa was directed against HCV core protein (Fig. 1B). The patient had HCV viremia (type 1a) and HHV-8 viremia (subtype C). Reverse-transcriptase polymerase-chain-reaction (PCR) and immunofluorescence studies revealed that his plasmablasts were infected with HCV and produced HCV core protein (Fig. 1C). Immunofluorescence and real-time (TaqMan) quantitative PCR studies indicated that 100 percent of plasmablasts were productively infected by HCV (≥300 viral copies per blast) (Fig. 1D).

In our patient, HCV and HHV-8 may have acted synergistically to cause plasma-cell leukemia, through the following sequence of events: HCV core-driven oligoclonal expansion of B lymphocytes; HCV infection of an HCV core–specific B-cell clone and monoclonal expansion of the core–specific, core-producing clone; monoclonal–plasmablast expansion after blockade of plasmacytic differentiation due to a PAX-5 rearrangement; and accelerated plasmablast expansion after infection by HHV-8 or reactivation of latent HHV-8 infection. Since patients may benefit from antiviral therapy,4 we propose that in cases of unusual presentation of B-lineage disease, the presence of B-cell–tropic transforming viruses should be investigated.
Enclosed you will find a set of Combo Cards – cards that highlight various ARV combinations a doctor may prescribe. Gilead provided an unrestricted educational grant to Smart and Strong for development of these types of cards. They have recently been mailed to over 4,000 physicians treating HIV.

These cards are being sent to you for your information only and are not to be used for detailing purposes.

If you have any questions, please call me at 650-522-5812.
Name: Viread (tenofovir) • Class: Nucleotide (NtRTI)
Dose: one 300 mg tablet once a day

Name: Ziagen (abacavir) • Class: Nucleoside (NRTI)
Dose: one 300 mg tablet twice a day

Name: Sustiva (efavirenz) • Class: Non-Nucleoside (NNRTI)
Dose: one 600 mg tablet once a day
SCHEDULING
Your usual activities, such as when you wake up, eat and go to bed, will affect how you take this combo. Ziagen and Sustiva can be taken with or without food, but you should avoid high-fat meals. Viread should be taken with food or a meal. Possible Schedule: Take one Ziagen and one Viread during breakfast. Then take one Ziagen and one Sustiva at bedtime.

ADHERENCE TIPS
It is very important to take your drugs according to a schedule designed by you and your doctor. This will keep the level of drug in your body as steady and effective as possible and decrease your chances of developing drug resistance. Make adherence—staying on schedule—easier by having a supply of medication with you at all times. Divide up daily doses at the beginning of each week. If you miss a dose, don’t take two doses at once. If it’s near the time of the next dose, skip the missed dose and then return to your regular schedule. If you have problems with adherence or side effects, don’t cut back or stop—talk to your doctor.

SIDE EFFECTS
Ziagen can cause a severe allergic reaction, usually during the first two to six weeks you are taking it. Symptoms include: abdominal pain, difficulty breathing, fever, nausea, rash or vomiting. If you think you may be having this reaction, stop taking Ziagen and call your doctor immediately. Side effects of this combo may include: Short-term: diarrhea, dizziness, drowsiness, headache, gas, increase in liver enzymes, loss of appetite, nausea or vomiting, trouble sleeping and vivid or unusual dreams. Long-term: lactic acidosis (a build-up of acid in the blood). Long-term use of HIV medications may cause lipodystrophy (abnormal fat distribution). Do not take Sustiva if you are, or are trying to become, pregnant.

INTERACTIONS
Your HIV combo may interact dangerously with other medications you are taking. In particular, Sustiva may have negative effects with methadone, certain antidepressants, oral contraceptives, St. John’s Wort, and medications for allergies, headache and stomach problems. Inform your doctor and pharmacist about every medicine you take, including over-the-counter drugs, vitamins, supplements and herbs.
FYI

† Name: Viread (tenofovir) • Class: Nucleotide (NRTI)
Dose: one 300 mg tablet once a day

‡ Name: Epivir (3TC) • Class: Nucleoside (NRTI)
Dose: two 150 mg tablets once a day (or one 150 mg tablet twice a day)

◊ Name: Invirase (saquinavir, hard gel capsule) • Class: Protease Inhibitor (PI)
Dose: eight 200 mg capsules once a day

◊ Name: Norvir (ritonavir) • Class: Protease Inhibitor (PI)
Dose: one 100 mg capsule once a day
SCHEDULING
Your usual activities, such as when you wake up, eat and go to bed, will affect how you take this combo. Epivir can be taken with or without food and can be taken once a day if instructed by your doctor. Viread, Inravase and Norvir should be taken with food or a meal. Since Norvir raises Inravase levels, you may use the hard-gel capsules rather than the soft-gel (called Fortovase) if instructed by your doctor.  
• Possible Schedule: Take one Viread, two Epivir, eight Inravase and one Norvir during dinner.

ADHERENCE TIPS
It is very important to take your drugs according to a schedule designed by you and your doctor. This will keep the level of drug in your body as steady and effective as possible and decrease your chances of developing drug resistance.  
• Make adherence—staying on schedule—easier by having a supply of medication with you at all times. Divide up daily doses at the beginning of each week.  
• If you miss a dose, don't take two doses at once. If it's near the time of the next dose, skip the missed dose and then return to your regular schedule.  
• If you have problems with adherence or side effects, don't cut back or stop—talk to your doctor.

SIDE EFFECTS
Side effects of this combo may include: Short-term: abdominal pain, diarrhea, dizziness, fatigue, headache, gas, loss of appetite, nausea or vomiting, trouble sleeping, numbness or tingling in mouth, fingers, hands or feet, and an increase in liver enzymes, cholesterol and triglycerides. Long-term: diabetes, lactic acidosis (a build-up of acid in the blood) and pancreatitis (indicated by abdominal pain, diarrhea, nausea or vomiting—drinking alcohol increases your risk).  
• Long-term use of HIV medications may cause lipodystrophy (abnormal fat distribution).

INTERACTIONS
Your HIV combo may interact dangerously with other medications you are taking.  
• In particular, Inravase and Norvir may have negative effects with street or party drugs, certain antibiotics, antifungals, blood thinners, oral contraceptives, St. John's Wort, sedatives and medications for allergies, cholesterol, erectile dysfunction, headache, heart and stomach problems, and TB.  
• Inform your doctor and pharmacist about every medicine you take, including over-the-counter drugs, vitamins, supplements and herbs.

For more info: www.ComboCards.com
FYI
1. Name: Viread (tenofovir) • Class: Nucleotide (NtRTI)
   Dose: one 300 mg tablet once a day
2. Name: Epivir (3TC) • Class: Nucleoside (NRTI)
   Dose: one 150 mg tablet twice a day or two 150 mg tablets once a day
3. Name: Viramune (nevirapine) • Class: Non-Nucleoside (NNRTI)
   Dose: one 200 mg tablet twice a day or two 200 mg tablets once a day
SCHEDULING

Your usual activities, such as when you wake up, eat and go to bed, will affect how you take this combo. Epivir and Viramune can be taken with or without food and can be taken once a day if instructed by your doctor. Viread should be taken with food or a meal. Viramune is taken at half dose (one pill per day instead of two) for the first 14 days. • Possible Schedule: For the first two weeks: Take one Epivir and one Viramune during breakfast; then take one Viread and one Epivir during dinner. After the first two weeks: Take one Epivir and one Viread during breakfast; then take one Viread, one Epivir and one Viramune during dinner.

ADHERENCE TIPS

It is very important to take your drugs according to a schedule designed by you and your doctor. This will keep the level of drug in your body as steady and effective as possible and decrease your chances of developing drug resistance. • Make adherence—staying on schedule—easier by having a supply of medication with you at all times. Divide up daily doses at the beginning of each week. • If you miss a dose, don’t take two doses at once. If it’s near the time of the next dose, skip the missed dose and then return to your regular schedule. • If you have problems with adherence or side effects, don’t cut back or stop—talk to your doctor.

SIDE EFFECTS

Side effects of this combo may include: Short-term: diarrheas, fatigue, headache, gas, increase in liver enzymes (frequent monitoring during the first 12 weeks is advised), loss of appetite, nausea or vomiting, and rash. Long-term: lactic acidosis (a build-up of acid in the blood). • Long-term use of HIV medications may cause lipodystrophy (abnormal fat distribution).

INTERACTIONS

Your HIV combo may interact dangerously with other medications you are taking. • In particular, Viramune may have negative effects with methadone, certain antidepressants, antifungals, oral contraceptives, St. John’s Wort, and medications for allergies, headache and stomach problems. • Inform your doctor and pharmacist about every medicine you take, including over-the-counter drugs, vitamins, supplements and herbs.
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Name: Viread (tenofovir) • Class: Nucleotide (NtRTI)
Dose: one 300 mg tablet once a day

Name: Epivir (3TC) • Class: Nucleoside (NRTI)
Dose: one 150 mg tablet twice a day

Name: Ziagen (abacavir) • Class: Nucleoside (NRTI)
Dose: one 300 mg tablet twice a day
### SCHEDULING

Your usual activities, such as when you wake up, eat and go to bed, will affect how you take this combo. Epivir and Ziagen can be taken with or without food. Viread should be taken with food or a meal. • Possible Schedule: Take one Epivir and one Ziagen during breakfast; then take one Viread, one Epivir and one Ziagen during dinner.

### ADHERENCE TIPS

It's very important to take your drugs according to a schedule designed by you and your doctor. This will keep the level of drug in your body as steady and effective as possible and decrease your chances of developing drug resistance. • Make adherence—staying on schedule—easier by having a supply of medication with you at all times. Divide up daily doses at the beginning of each week. • If you miss a dose, don't take two doses at once. If it's near the time of the next dose, skip the missed dose and then return to your regular schedule. • If you have problems with adherence or side effects, don't cut back or stop—talk to your doctor.

### SIDE EFFECTS

Ziagen can cause a severe allergic reaction, usually during the first two to six weeks you are taking it. Symptoms include: abdominal pain, difficulty breathing, fever, nausea, rash or vomiting. If you think you may be having this reaction, stop taking Ziagen and call your doctor immediately.

- Side effects of this combo may include: Short-term: diarrhea, fatigue, gas, headache, loss of appetite and nausea or vomiting. Long-term: lactic acidosis (a build-up of acid in the blood). • Long-term use of HIV medications may cause lipoatrophy (abnormal fat distribution).

### INTERACTIONS

Your HIV combo may interact dangerously with other medications you are taking. • Inform your doctor and pharmacist about every medicine you take, including over-the-counter drugs, vitamins, supplements and herbs.
FYI

1 Name: Viread (tenofovir) • Class: Nucleotide (NRTI)
   Dose: one 300 mg tablet once a day

2 Name: Epivir (3TC) • Class: Nucleoside (NRTI)
   Dose: two 150 mg tablets once a day or one 150 mg tablet twice a day

3 Name: Sustiva (efavirenz) • Class: Non-Nucleoside (NNRTI)
   Dose: one 600 mg tablet once a day
SCHEDULING
Your usual activities, such as when you wake up, eat and go to bed, will affect how you take this combo. Viread should be taken with food or a meal. Epivir can be taken with or without food and can be taken once a day if instructed by your doctor. Sustiva can be taken with or without food, but you should avoid high-fat meals. * Possible Schedule: Take one Viread, two Epivir and one Sustiva with a low-fat snack at bedtime.

ADHERENCE TIPS
It is very important to take your drugs according to a schedule designed by you and your doctor. This will keep the level of drug in your body as steady and effective as possible and decrease your chances of developing drug resistance. * Make adherence—staying on schedule—easier by having a supply of medication with you at all times. Divide up daily doses at the beginning of each week. * If you miss a dose, don’t take two doses at once. If it’s near the time of the next dose, skip the missed dose and then return to your regular schedule. * If you have problems with adherence or side effects, don’t cut back or stop—talk to your doctor.

SIDE EFFECTS
Side effects of this combo may include: Short-term: diarrhea, dizziness, drowsiness, fatigue, headache, gas, increase in liver enzymes, loss of appetite, nausea or vomiting, trouble sleeping and vivid or unusual dreams. Long-term: lactic acidosis (a build-up of acid in the blood). * Long-term use of HIV medications may cause lipodystrophy (abnormal fat distribution). * Do not take Sustiva if you are, or are trying to become, pregnant.

INTERACTIONS
Your HIV combo may interact dangerously with other medications you are taking. * In particular, Sustiva may have negative effects with methadone, certain antidepressants, oral contraceptives, St. John’s Wort, and medications for allergies, headache and stomach problems. * Inform your doctor and pharmacist about every medicine you take, including over-the-counter drugs, vitamins, supplements and herbs.
COMBO CARDS

**COMBIVIR®**  
**INVIRASE®**  
**NORVIR®**

### AM

1. **Combivir** (300 mg zidovudine plus 150 mg lamivudine)  
   - **Class:** Nucleoside (NRTI)  
   - **Dose:** one tablet twice a day

### PM

2. **Invirase** (saquinavir, hard gel capsule)  
   - **Class:** Protease Inhibitor (PI)  
   - **Dose:** five 200 mg capsules twice a day

3. **Norvir** (ritonavir)  
   - **Class:** Protease Inhibitor (PI)  
   - **Dose:** one 100 mg capsule twice a day

### FYI

- **Name:** Combivir (300 mg zidovudine plus 150 mg lamivudine)  
  - **Class:** Nucleoside (NRTI)  
  - **Dose:** one tablet twice a day
- **Name:** Invirase (saquinavir, hard gel capsule)  
  - **Class:** Protease Inhibitor (PI)  
  - **Dose:** five 200 mg capsules twice a day
- **Name:** Norvir (ritonavir)  
  - **Class:** Protease Inhibitor (PI)  
  - **Dose:** one 100 mg capsule twice a day
SCHEDULING
Your usual activities, such as when you wake up, eat and go to bed, will affect how you take this combo. Combidr can be taken with or without food. Invirase and Norvir should be taken with food or a meal. Since Norvir raises Invirase levels, you may use the hard-gel capsules rather than the larger soft-gel (called Fortovase) if instructed by your doctor.

Possible Schedule: Take one Combivir, five Invirase and one Norvir during breakfast; then take one Combivir, five Invirase and one Norvir during dinner.

ADHERENCE TIPS
It is very important to take your drugs according to a schedule designed by you and your doctor. This will keep the level of drug in your body as steady and effective as possible and decrease your chances of developing drug resistance.

Make adherence—staying on schedule—easier by having a supply of medication with you at all times. Divide up daily doses at the beginning of each week. If you miss a dose, don’t take two doses at once. If it’s near the time of the next dose, skip the missed dose and then return to your regular schedule.

If you have problems with adherence or side effects, don’t cut back or stop—talk to your doctor.

SIDE EFFECTS
Side effects of this combo may include:

Short-term: abdominal pain, diarrhea, diziness, fatigue, headache, loss of appetite, muscle or joint pain, nausea or vomiting, trouble sleeping, weakness, numbness or tingling in mouth, fingers, hands or feet, and an increase in liver enzymes, cholesterol and triglycerides. Long-term: anemia (a decrease in red blood cells), diabetes, lactic acidosis (a build-up of acid in the blood), neutropenia (a decrease in white blood cells) and pancreatitis (indicated by abdominal pain, diarrhea, nausea or vomiting—drinking alcohol increases your risk).

Long-term use of HIV medications may cause lipodystrophy (abnormal fat distribution).

INTERACTIONS
Your HIV combo may interact dangerously with other medications you are taking. In particular, Invirase and Norvir may have negative effects with street or party drugs, certain antibiotics, antifungals, blood thinners, oral contraceptives, St. John’s Wort, sedatives and medications for allergies, cholesterol, erectile dysfunction, headaches, heart and stomach problems, and TB. Inform your doctor and pharmacist about every medicine you take, including over-the-counter drugs, vitamins, supplements and herbs.
COMBO CARDS

Combivir®
Invirase®
Kaletra®

FYI
1 Name: Combivir (300 mg zidovudine plus 150 mg lamivudine)
  Class: Nucleoside (NRTI)  
  Dose: one tablet twice a day
2 Name: Invirase (saquinavir, hard gel capsule)  
  Class: Protease Inhibitor (PI)  
  Dose: five 200 mg capsules twice a day
3 Name: Kaletra (133.3 mg lopinavir plus 33.3 mg ritonavir)
  Class: Protease Inhibitor (PI)  
  Dose: three capsules twice a day
SCHEDULING
Your usual activities, such as when you wake up, eat and go to
bed, will affect how you take this combo. Epivir can be taken with or
without food. Virade and Kaletra should be taken with food or a meal.
Possible Schedule: Take one Epivir and three Kaletra during breakfast;
then take one Virade, one Epivir and three Kaletra during dinner.

ADHERENCE TIPS
It is very important to take your drugs according to a schedule designed
by you and your doctor. This will keep the level of drug in your body as
steady and effective as possible and decrease your chances of develop-
ing drug resistance. • Make adherence—staying on schedule—easier by
having a supply of medication with you at all times. Divide up daily doses
at the beginning of each week. • If you miss a dose, don't take two
doses at once. If it's near the time of the next dose, skip the missed dose
and then return to your regular schedule. • If you have problems with
adherence or side effects, don't cut back or stop—talk to your doctor.

SIDE EFFECTS
Side effects of this combo may include: Short-term: abdominal pain, diar-
rhea, fatigue, headache, gas, loss of appetite, nausea or vomiting, trouble
sleeping, and an increase in liver enzymes, cholesterol and triglycerides.
Long-term: diabetes, lactic acidosis (a build-up of acid in the blood) and
pancreatitis (indicated by abdominal pain, diarrhea, nausea or vomiting—
drinking alcohol increases your risk). • Long-term use of HIV medications
may cause lipodystrophy (abnormal fat distribution).

INTERACTIONS
Your HIV combo may interact dangerously with other medications you are
taking. • In particular, Kaletra may have negative effects with street or
party drugs, certain antibiotics, antifungals, blood thinners, oral contra-
ceptives, St John's Wort, sedatives, and medications for allergies, chole-
sterol, erectile dysfunction, headache, heart and stomach problems, and
TB. • Inform your doctor and pharmacist about every medicine you take,
including over-the-counter drugs, vitamins, supplements and herbs.
Dear Dr. Coleman:

This letter notifies Gilead Sciences (Gilead) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional activities that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, representatives of Gilead made both false and misleading oral statements about Viread at Gilead’s promotional exhibit booth at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) held in Chicago, Illinois in December 2001.

False or Misleading Statements and Minimization of Important Risk Information

Gilead’s representatives engaged in false and misleading promotional activities about a boxed warning in Viread’s approved product labeling (PI). The boxed warning states that “Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals.”

One Gilead representative failed to provide any risk information and instead made the following false or misleading statements about Viread to DDMAC reviewers at Gilead’s promotional exhibit booth at ICAAC:

- “no toxicities”
- “extremely safe”
- “extremely well-tolerated”
Two additional Gilead representatives made the following statements:

- The boxed warning is a "product class warning, and there are no problems but it was put into the PI as a 'wait and see' warning."
- Viread "does not affect mitochondria; therefore, you would not expect to see lactic acidosis."
- The warning "is a class effect" and "our PI is the only one that does not name the drug because Viread is a nucleotide, not a nucleoside."

These statements are in violation of the Act because they minimize the boxed warning for Viread and misleadingly suggest that the drug is safer than has been demonstrated by substantial evidence. In fact, there have been case reports of lactic acidosis in patients receiving Viread in clinical trials and the expanded access program. Additionally, although in vitro studies may suggest a lack of mitochondrial toxicity, it is misleading to suggest that these conclusions from nonclinical studies have clinical significance when such has not been demonstrated by substantial evidence. Furthermore, Viread functions as a nucleoside analogue and, therefore, carries the same class warnings as other nucleoside reverse transcriptase inhibitors (NRTIs).

Furthermore, these statements are inconsistent with other risk information in the PI. Viread's PI contains a warning not to administer the drug to patients with renal insufficiency, and various precautions, such as potential drug interactions when Viread is concomitantly administered with didanosine or with drugs that reduce renal function or compete for active tubular secretion. The PI also states that treatment-related adverse events that occurred in patients receiving Viread include mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence.

**Overstatement of Efficacy**

A fourth Gilead representative also engaged in false or misleading promotional activities about the efficacy of Viread. Specifically, this representative stated that Viread "is approved for a broad indication" and characterized it as a "miracle drug." In fact, Viread was approved by the Food and Drug Administration under accelerated approval status, and the clinical benefit of Viread in HIV patients has not yet been determined. Moreover, there are substantial limitations to Viread's indication as stated in the PI:

"VIREAD is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in a controlled study of VIREAD of 24 weeks duration and in a controlled, dose ranging study of VIREAD of 48 weeks duration. Both studies were conducted in treatment experienced adults with evidence of HIV-1 viral replication despite ongoing antiretroviral therapy. Studies in antiretroviral naïve patients are ongoing; consequently the risk-benefit ratio for this population has yet to be determined.

Additional important information regarding the use of VIREAD for the treatment of HIV-1 infection:
• There are no study results demonstrating the effect of VIREAD on clinical progression of HIV.
• The use of VIREAD should be considered for treating adult patients with HIV strains that are expected to be susceptible to tenofovir as assessed by laboratory testing or treatment history.

The above oral statements made by the Gilead representative are misleading, and therefore in violation of the Act because they overstate the efficacy of Viread, and fail to communicate material facts with respect to the limitations of its indication.

Requested Actions

Gilead should immediately cease making such violative statements and should cease the distribution or use of any promotional materials for Viread that contain the same or similar violative statements. Gilead should submit a written response to DDMAC on or before March 28, 2002, describing its intent and plans to comply with the above. In its letter to DDMAC, Gilead should include the date on which this and other similarly violative materials were discontinued.

Gilead should direct its response to me by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this matter, please refer to MACMIS ID #10666 in addition to the NDA number. DDMAC reminds Gilead that only written communications are considered official.

Sincerely,

Laura L. Pincock, Pharm.D.
LT, USPHS
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Laura Pincock
3/14/02 03:36:28 PM
Region Breakouts  
Thursday, June 26, 2003  
Time: 1:00PM – 4:30PM

### HIV Division

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### Hep/Onc Division

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Cheri Beth White and Lisa Yetzer

**OBJECTIONS WORKSHOP RESPONSES: data to use in response to the following objections.**

1. So Viread is now causing renal problems...I knew this would happen.
   - Reassure the physician that Viread is not Adefovir. In the controlled clinical trials there has been no evidence of renal toxicities. Study 910 (rollover of 902/907) has 670 patients out 4 years. Study 903 has 299 patients out 2 years.
   - Remind physician that we amended our PI sheet to include caution when using Viread in patients with a creatinine <60, and recommend a dose interval adjustment in patients with creatinine <50. Medical Information will send you the dose interval information. Also recommend not using Viread in patients taking concomitant nephrotoxic drugs.
   - If the physician brings it up, discuss the Reyes and Blick posters to defend Viread. Point out that the patients in the Blick study (3) had previous nephrotoxicity with Adefovir at high doses.

When phosphorus supplements were added to Viread the creatinine levels went back to normal range in the two patients who continued on Viread.
   - Focus on using FTC and Viread to break up the Combivir.
   - Key in on the AZT toxicities associated with Combivir, i.e. anemia, headache, etc. If the patient has anemia you may have to add an additional drug like Procrit that increases the numbers of pills and cost to the patient.
   - Use study 903 to show the excellent safety and durability of Viread in naïve patients. Show the low mitochondrial side effects with Viread and point out that FTC is 24 fold less efficiently incorporated in the mDNA polymerase.
   - Discuss if appropriate the ACTG 5095 data and the why it would make more sense to use Viread/FTC.
   - Point out with Viread/FTC you can create a truly q day regimen. With the long half life of Viread (17 hrs) and FTC (10 hours) and the 39 hour intracellular half life of FTC, FTC/Viread offer a more forgiving regimen.
   - Since this scenario include a large population of women; stress the pregnancy category B of both Viread and FTC.

*OVER LOOK PATTERN ON VIREAD - MORE THEN CLINICAL TRIAL*
4. My patients tolerate Zerit and I don’t see the lipoatrophy develop in them.

- Go through all the data to show the excellent efficacy of Viread and D4T. Show the significant differences in the D4T vs Viread arms for lipids, mitochondrial changes, body weight changes, and total limb fat. Show how the differences become more pronounced between week 48 and 96. Since the physician is concerned about lipid, highlights that 5 times as many patients had to add a lipid lowering agent vs Viread. This increases the pill burden and potentially the cost to the patient.
- Show the half-life of Viread and FTC with EFV for a more forgiving truly q day regimen.
- Use the FTC 302 study to show the M184V mutation developed less in FTC arm vs 3TC, 30% vs 65%.
- In using EFV with FTC/Viread you are still sparing the PI class. By using a TAM sparing regimen including FTC/Viread you are providing the patient more options. Remind the physician that the K65R occurs in less that 3% of patients in naive and experienced patients.
- Show FTC 301 that FTC provided superior efficacy and less resistance that D4T. The DSMB gave the D4T patients the option of switching to FTC at week 24. At week 48, FTC continued to show superior efficacy to D4T.
Dear Dr. Martin:

This Warning Letter objects to Gilead Sciences, Inc.'s ("Gilead") promotional activities for Viread (tenofovir disoproxil fumarate) Tablets. Through routine monitoring and surveillance, the Food and Drug Administration's ("FDA" or the "Agency") Division of Drug Marketing, Advertising, and Communications ("DDMAC") has concluded that Gilead's promotion of Viread violates the Federal Food, Drug, and Cosmetic Act (the "Act") and its implementing regulations.

Specifically, a representative of Gilead made oral representations at Gilead's promotional exhibit booth during the 15th National HIV/AIDS Update Conference in Miami, Florida, on March 31 - April 2, 2003, that minimized important risk information and broadened the indication for Viread. Your failure to disclose the fatal risks of lactic acidosis and severe hepatomegaly with steatosis reported with the use of nucleoside analogues raises significant public health and safety concerns. This conduct is particularly troubling because the more than 1,500 attendees of this conference included social workers, AIDS educators, and patients with HIV/AIDS, and you had previously been warned not to engage in such activities.

Background

Viread was approved under the Subpart H (accelerated approval) regulations, 21 CFR 314.510, on October 26, 2001, for the following indication:

Viread is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in a controlled study of Viread of 24 weeks duration and in a controlled, dose ranging study of Viread of 48 weeks duration. Both studies were conducted in treatment experienced adults with evidence of HIV-1 viral replication despite ongoing antiretroviral therapy. Studies in antiretroviral naive patients are ongoing; consequently, the risk-benefit ratio for this population has yet to be determined. There are no study results demonstrating the effect of Viread on clinical progression of HIV. The use of Viread should be considered for treating adult patients...
with HIV strains that are expected to be susceptible to tenofovir as assessed by laboratory
testing or treatment history.

Viread is a nucleotide that shares similar structural and functional properties with nucleoside
analogues approved for the treatment of HIV infection, such as its prodrug status that requires
metabolic activation by cellular enzymes to form the pharmacologically active metabolite, the
triphosphate form. The triphosphate form competes with the physiological substrate dATP for
incorporation into nascent DNA, and causes chain termination due to lack of a sugar moiety.
Viread does not require the initial phosphorylation by the nucleoside kinase of the host cells, a
property that distinguishes it from currently approved nucleoside analogues. However, this
property of Viread has not been demonstrated to FDA to convey a clinical advantage over
nucleoside analogues.

Because Viread functions as a nucleoside analogue, the approved product labeling (PI) for
Viread includes a box warning that states, "Lactic acidosis and severe hepatomegaly with
steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone
or in combination with other antiretrovirals." This warning is identical to the labeling warnings
for nucleoside analogues. In vitro studies may suggest a lack of mitochondrial toxicity, but we
are not aware of any studies that demonstrate that these results are predictive of in vivo lack of
toxicity. Moreover, lactic acidosis has been observed in clinical trials and in your expanded
access program.

On October 26, 2001, a conference call took place between Dr. Jean-Ah Choi from DDMAC
and Dr. [redacted] Dr. Choi provided advisory comments regarding proposed launch materials
for Viread. Gilead noted the following points in its November 7, 2001,
correspondence/written meeting minutes to DDMAC:

- "Dr. Choi advised that referring to Viread as a nucleotide in a way that conveyed that
  this confers an advantage over other drugs was not acceptable. In promotional
  materials references to the mechanistic descriptor "nucleotide analog" will be used
  without conveying that this is an advantage."

- "Comparison statements (safer than other regimens) are not supported by data and
  would be acceptable only if studies have been performed evaluating those questions
  specifically."

- Dr. Choi advised Gilead to include the "most common and most serious findings"
  regarding safety (Viread's PI contains a warning not to administer the drug to
  patients with renal insufficiency, and various precautions, such as potential drug
  interactions when Viread is concomitantly administered with didanosine or with
  drugs that reduce renal function or compete for active tubular secretion. The PI also
  states that treatment-related adverse events that occurred in patients receiving
  Viread include mild to moderate gastrointestinal events, such as nausea, diarrhea,
  vomiting, and flatulence). The most serious findings are the boxed warnings for lactic
  acidosis and severe hepatomegaly with steatosis.

- Dr. Choi informed Gilead that "all promotional information describing the activity of
  Viread should include the limitations of the data as represented in the indication."

On March 14, 2002, DDMAC issued an Untitled Letter to Gilead regarding promotional
activities that violate the Act. The letter explained that representatives of Gilead made both
false and misleading oral statements about Viread at Gilead's promotional exhibit booth at the
41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) held in

Specifically, a Gilead representative failed to provide any risk information and made false or
misleading representations by describing Viread as "extremely safe," "no toxicities," and
"extremely well-tolerated." Two other Gilead representatives minimized the important risk

http://www.fda.gov/foi/warning_letters/g4180d.htm 3/11/2004
information for Viread by referring to the boxed warning as a "product class warning" and "class effect." The Gilead representatives described Viread as a "nucleotide, not a nucleoside," thereby suggesting that the same safety issues do not apply. Additionally, the representatives claimed that Viread "does not affect the mitochondria," thereby implying that lactic acidosis would not be expected with Viread. Furthermore, a fourth Gilead representative grossly overstated the efficacy of Viread by characterizing it as a "miracle drug" that "is approved for a broad indication."

On March 21, 2002, Gilead responded to DDMAC's March 14, 2002, Untitled Letter. Your letter states that "Gilead has issued a memorandum to U.S. sales and marketing personnel, medical affairs staff, and all Gilead attendees at ICAAC" regarding the violations outlined in DDMAC's March 14, 2002, letter and "reminding them that such violations are inconsistent with Gilead's promotional policies." Additionally, your letter states that "Gilead takes very seriously the policy that all oral and written product promotion accurately represents the approved indication and labeling, and provides fair balance of risks and benefits of the product," and that the letter "constitutes Gilead's commitment to ensure that future violative statements are not made in the promotion of Viread." Despite your assurance that violative promotional activities would cease, your sales representative continues to violate the Act.

Promotional Activities by Gilead's Sales Representative

On April 2, 2003, at Gilead's promotional exhibit booth during the 15th National HIV/AIDS Update Conference, your sales representative made oral statements that minimized the risk information and broadened the indication for Viread.

Minimization of Important Risk Information
Your sales representative greatly minimized the important safety information for Viread. Your representative failed to provide any risk information from Viread's boxed warning concerning reported fatal cases of lactic acidosis and severe hepatomegaly with steatosis linked to the use of nucleoside analogues. Your representative claimed that the boxed warning is a "class effect warning on all nucleoside analogues" and did not apply to Viread. Furthermore, your representative referred to the totality of the adverse reactions associated with Viread as "benign." By failing to include any of the important risk information, Gilead misleadingly suggests that Viread is safer than has been demonstrated by substantial evidence or substantial clinical experience. This omission of the boxed warning together with other important risk information for Viread is particularly concerning given the serious risks associated with the drug.

Your representative also stated that because Viread is a nucleotide, not a nucleoside, it is "more potent," has "fewer side effects," and is "safer." As discussed above, it is misleading to suggest that Viread confers any clinical advantages over nucleoside analogues without supporting data. Moreover, Viread functions as a nucleoside analogue and, therefore, carries the same warnings as nucleoside analogues. Furthermore, the Agency is not aware of any data from head-to-head clinical trials to substantiate claims of more favorable safety or efficacy with Viread over other drug products.

Broadened Indication
Your representative misleadingly broadened the indication for Viread. Your representative failed to convey that Viread is only approved for use in combination with other antiretroviral agents. It is imperative to emphasize that patients take Viread as part of an antiretroviral combination regimen because monotherapy can lead to rapid development of resistant virus, thereby decreasing the therapeutic effectiveness of the drug and reducing the susceptibility of the HIV virus to the drug. Emergence of drug resistance is a major concern in the treatment of HIV patients.

Your sales representative also stated that Viread "improves lipid parameters." FDA is not aware of substantial evidence or substantial clinical experience that supports the claim that Viread has a positive impact on patients' lipid profiles.
These oral statements by your representative recommending or suggesting use of Viread for a use other than that for which FDA has reviewed safety and effectiveness data create a new "intended use" for which adequate directions must be provided in approved product labeling. 21 U.S.C. 352(f)(1); 21 C.F.R 201.5, 201.100, 201.128. Absent such directions, your product is misbranded. 21 U.S.C. 352(f)(1).

Conclusions and Requested Actions

Gilead's sales representatives have repeatedly omitted or minimized material facts regarding the safety profile of Viread, and have broadened Viread's approved indication. Due to the significant public health and safety concerns raised by these repetitive promotional activities, we request that you provide a detailed response to the issues raised in this Warning Letter. This response should contain an action plan that includes:

1) The date on which Gilead ceased dissemination of the above statements and all promotional materials that contain the same or similar statements.
2) A plan of action to disseminate accurate and complete information to the audience(s) that received the promotional statements described above.
3) A written statement of your intent to comply with "1" and "2" above.
4) A commitment to retrain your sales representatives to ensure that their promotional activities comply with your firm's policies and with applicable requirements of the Act and regulations, and an explanation of why/how you expect this retraining to succeed.

Gilead should submit a written response to DDMAC by August 12, 2003, describing its intent and plan to comply with DDMAC's request. If you have any questions or comments, please contact Debi Tran, Pharm.D. or Lesley Frank, Ph.D., J.D. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857.

We remind you that only written communications are considered official. In all future correspondence regarding this particular matter please refer to MACMIS ID 11723 in addition to the NDA number.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Viread and may determine that additional measures will be necessary to address other conduct.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,
(See appended electronic signature page)
Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing, Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/S/
Barbara Chong
7/29/03 03:26:37 PM
Signed for Thomas W. Abrams

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FDA/Freedom of Information

http://www.fda.gov/foi/warning_letters/g4180d.htm 3/11/2004
EXHIBIT G
November 7, 2003

IMPORTANT CORRECTION OF DRUG INFORMATION

Dear emiAR Miami Conference Attendee:

The Food & Drug Administration (FDA)’s Division of Drug Marketing, Advertising, and Communications (DDMAC) has asked us to contact you because Gilead recently received a Warning Letter containing our HIV drug product, Videx® (stavudine disoproxil fumarate) Tablets.

The Warning Letter cites a Gilead sales representative as having made misleading oral statements in the promotion of Videx at Gilead’s exhibit booth during the American Foundation for AIDS Research (emAR)’s 15th Annual National HIV/AIDS Update Conference held in Miami, Florida from March 31 – April 2, 2005. This letter provides accurate information about Videx and corrects certain information as cited in the Warning Letter.

- Serious, potentially fatal risks have been associated with the use of Videx and other drugs in this class. Videx may cause a buildup of lactic acid in the blood (lactic acidosis) and enlargement of the liver with fat accumulation in liver cells (severe hepatomegaly with steatosis) alone or in combination with other anti-HIV medications. According to the Warning Letter, Gilead’s representative did not tell attendees about these serious and potentially fatal risks. When questioned about these risks, Gilead’s representative claimed that they did not apply to Videx and referred to the adverse reactions associated with Videx as “benign”.

- Videx is a nucleoside reverse transcriptase inhibitor. It belongs to the same class and carries the same serious risks as antiretroviral drugs known as nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). The fact that Videx is a nucleoside does not make it better or safer than NRTIs. According to the Warning Letter, Gilead’s representative claimed that because Videx is a nucleoside, not a nucleotide, it is “more potent”, “safer” and has “fewer side effects” than NRTIs. (Please see the enclosed package insert and patient package insert for a listing of the possible side effects of Videx).
- Viread is approved for use only in combination with other anti-HIV medicines to treat people with HIV-1 infection. Use of Viread alone (monotherapy) can lead to the rapid development of resistance making the virus harder to treat. According to the Warning Letter, Gilead's representative failed to convey that Viread is only approved for use in combination with other anti-HIV medicines.

- Viread has not been proven to improve cholesterol levels (lipid parameters). According to the Warning Letter, Gilead's representative claimed that Viread "improves lipid parameters".

A copy of the full Prescribing Information and Patient Package Insert for Viread is enclosed for your reference. If you have any additional questions, please contact the Gilead Medical Information Department at 1-800-GILEAD-5, Option 2.

Thank you.

[Signature]

John C. Martin, PhD
President and Chief Executive Officer